# BRIEFING BOOK FOR ARTHRITIS ADVISORY COMMITTEE MEETING

# REGN475

***March 2012***

REGENERON

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| ANOVA | Analysis of variance |
| AUC | Area under the curve |
| CI | Confidence interval |
| CTX | Carboxy-terminal collagen crosslinks |
| DMM | Destabilization of the medial meniscus |
| ECG | Electrocardiogram |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FIH | First-in-human |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| HSAN | Hereditary sensory and autonomic neuropathy |
| ICF | Informed consent form |
| IDMC | Independent data monitoring committee |
| IND | Investigational New Dug |
| IRB | Institutional review board |
| ITT | Intention-to-treat |
| IV | Intravenous(ly) |
| IVRS | Interactive voice response system |
| LLOQ | Lower limit of quantification |
| LOCF | Last observation carried forward |
| LS | Least squares |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed-effect model repeated measures |
| NGF | Nerve growth factor |
| NRS | Numeric rating scale |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OA | Osteoarthritis |
| PBS | Phosphate-buffered saline |

| | |
|---|---|
| PGIC | Patient's Global Impression of Change |
| PK | Pharmacokinetic |
| QOL | Quality of life |
| RCT | Randomized-controlled trial |
| Regeneron | Regeneron Pharmaceuticals, Inc. |
| RPOA | Rapidly progressive osteoarthritis |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SC | Subcutaneous |
| SF-12 | Short-Form 12-Item Questionnaire |
| $t_{1/2}$ | Terminal half-life |
| TEAE | Treatment-emergent adverse event |
| TJR | Total joint replacement |
| TrkA | Tyrosine kinase type 1 |
| WOMAC | Western Ontario and McMaster Osteoarthritis Index |

# EXECUTIVE SUMMARY

Patients with pain have an unmet medical need for new therapeutics. Persistent pain represents a substantial and growing unmet medical need, affecting nearly half of all people seeking medical care in the United States. Persistent or inadequately treated pain has a profound impact on the quality of life (QOL) for millions of people worldwide, and costs an estimated $635 billion a year in lost productivity and medical costs (Institute of Medicine Report Brief 2011).

While a wide variety of analgesic medications are currently available, many patients with acute and chronic pain still do not receive adequate relief or are unable to tolerate therapy. The limitations of currently available analgesic therapies are well-known and include central nervous system effects, nausea and vomiting, gastrointestinal (GI) bleeding and ulceration, constipation, hepatotoxicity, cardiovascular events, renal toxicity, and potential for abuse and dependence. In 1999, it was estimated that approximately 103,000 hospitalizations and 16,500 deaths occur yearly in the United States as a result of nonsteroidal anti-inflammatory drug (NSAID)-related ulcer complications (Wolfe 1999).

The targeting of nerve growth factor (NGF) – a neurotrophin that has been known for decades - is the first potential advance in pain management in many years. An effective anti-NGF therapy has the potential to help those patients who are unable to achieve adequate pain relief with existing therapies and/or who are unable to tolerate or are not good candidates for existing therapies.

**Anti-NGF Therapy; a Novel Analgesic Approach:** Neurotrophins are a family of protein growth factors that play a role in the development, differentiation, survival and death of neuronal and non-neuronal cells (Chao 2006). The first neurotrophin to be identified was NGF, and its role in the development and survival of both peripheral and central neurons in the developing nervous system has been well characterized (Smeyne 1994; Crowley 1994).

In the adult, however, NGF is not required as a constitutive survival factor, but instead has other roles such as serving as a pain mediator by sensitizing nociceptive neurons (Pezet and McMahon 2006). Nerve growth factor expression is elevated in many acute and chronic painful conditions and NGF blockade has demonstrated efficacy in various animal models of pain. As a result, it was postulated that NGF blockade could produce pain relief via a novel mechanism, without the same limitations of many currently used analgesic medications.

REGN475 is a fully-human high-affinity monoclonal antibody (mAb) directed against NGF. The antibody is specific for NGF, and does not detectably bind to any other members of the neurotrophin family, which includes brain-derived neurotrophic factor, neurotrophin-3 (NT-3), and NT-4/5. By selectively blocking NGF, REGN475 has the potential to help those patients who are unable to achieve adequate pain relief with existing therapies and/or who are unable to tolerate or are not good candidates for existing therapies.

**REGN475 Efficacy**: Efficacy of REGN475 in osteoarthritis (OA) of the knee was explored via daily assessments of pain intensity. Assessment of changes in function, Patient's Global Impression of Change (PGIC) and QoL were conducted at specified clinic visits (Section 3.2.4.5).

All 3 dose levels of REGN475 (0.03, 0.1 and 0.3 mg/kg intravenous [IV]), were associated with greater improvement compared with placebo in walking knee pain, Standardized Total Western Ontario and McMaster Osteoarthritis Index (WOMAC) Score, WOMAC Subscales (Pain, Function, and Stiffness), and PGIC. The effects were generally greater and more prolonged with the 0.1 and 0.3 mg/kg dose levels than with the 0.03 mg/kg dose level.

REGN475 did not demonstrate efficacy in the relief of sciatic pain in a study of patients with moderate -to-severe sciatic pain (≥ 4 on the NRS), for a period of at least 2 weeks but no more than 16 weeks.

**REGN475 General Safety**: As of December 2010, 503 patients had been studied in the REGN475 clinical program. The data show an increased incidence of neurosensory symptoms, myalgia, and arthralgia. These appear early after treatment in susceptible individuals and seem to resolve by the end of the studies. In addition, peripheral edema has been seen with the anti-NGF agents. Similar findings have been described with other anti-NGF mAbs. The long-term consequences of these are unknown.

**Nerve Growth Factor Class Clinical Hold:** A safety signal was identified in the tanezumab database consisting of increased risk of unanticipated joint deterioration leading to total joint replacement (TJR). As a consequence, the tanezumab program was placed on clinical hold. Subsequent identification of an additional case in the fulranumab program led to the clinical hold being extended to the entire class.

**REGN475 Joint-Related AEs of Interest:** A total of 14 joint replacements were reported in 12 patients. At the time that the Clinical Hold was placed on the anti-NGF class in December 2010, a total of 2 joint replacements had been reported during the conduct of the REGN475 clinical program. Post-study follow-up of patients who had participated in REGN475 studies revealed an additional 12 joint replacements in 10 patients that took place after the studies had concluded.

An external review by an independent Adjudication Committee assessed that of the 14 joint replacement cases reported, 10 cases were considered to be consistent with the normal progression of OA. For the remaining 4 cases, only 1 was considered possible rapidly progressive osteoarthritis (RPOA): a patient with clinical features and MRI report consistent with subchondral insufficiency/fracture resulting in RPOA. None of the cases were considered to be osteonecrosis. There is no outcome information on TJR cases.

A review of bone or joint-related cases is provided in Section 4.

**Joint Related Safety for NGF Class:** Blinded adjudication committees for 2 other sponsors' anti-NGF mAbs have concluded that these molecules are associated with an increased risk of RPOA leading to TJR, but that there is not an increased risk for osteonecrosis. Analyses of the tanezumab data by its sponsor show that the risk of RPOA increases with tanezumab dose and with the concomitant use of chronic NSAIDs. Moreover, these joints may be associated with pathology that is atypical for OA and there is a question as to whether these occur in patients previously unknown to have OA. Outcome information on TJR cases is incomplete or missing.

**Proposal to Allow Lifting of Clinical Hold:** Clearly the database of patients developed by Regeneron and Sanofi prior to the clinical hold is too small to support or refute the idea that there is a risk of unanticipated joint damage during the use of REGN475. Therefore, although each of

these molecules is likely to differ in terms of epitope specificity and affinity for NGF and cross-reactivity for other neurotrophin family members, we believe it prudent to act as if the risks of unanticipated joint deterioration identified with the other anti-NGF mAbs may also be a risk of REGN475. We are interested in learning more about those data at the public advisory committee that the Agency has scheduled.

However, a possible risk associated with anti-NGF treatment needs to be placed in the context of the unmet clinical need and the known toxicities of existing therapies. Not all OA patients achieve sufficient relief from NSAIDs at either the over-the-counter or prescription doses, and many patients are either not good candidates for NSAIDs (eg, due to difficult to manage hypertension, reduced renal function, history of upper gastrointestinal ulcers, cardiovascular disease, or a myriad of other conditions) or are not able to tolerate some of the symptomatic side effects of full-dose NSAID therapy. The symptomatic side effects of opioid therapy (nausea, constipation, somnolence, dry mouth), are also common complaints among patients and the primary reasons for discontinuing therapy. In addition, there are many patients who are awaiting joint replacement for periods of time or who are not candidates for joint replacement for medical or other reasons, and who must continue to struggle with pain and limited function on a daily basis. Moreover, because of the possibility that NSAIDs may interfere with bone healing, for those patients awaiting elective joint surgery, it may be desirable to control pain without NSAIDs. For non-OA pain conditions (eg patients with cancer, neuropathic, thermal injury, or visceral pain conditions), there is an unmet need for adequate analgesia.

Our position at Regeneron and Sanofi is that the data suggest a path forward for removal of the clinical hold and the resumption of studies based on a new framework. The current data, while providing evidence for the efficacy of anti-NGF therapy, is inadequate to support anti-NGF therapy as a general treatment for OA or for other painful conditions for which there are adequate treatments; the observed safety signals mentioned above need to be understood to a much greater degree before that could be the case. However, there may be a role for anti-NGF therapy in pain conditions where there is a high unmet need, ie, those for which there are no adequate alternatives. This is predicated on being able to demonstrate a clinically significant benefit over existing options and an acceptable safety profile such that a positive benefit/risk can be established within this context.

For REGN475, we propose a path forward, implementing the following strategies:

- **Informed Consent** of patients and appropriate communication of the data and potential risks to investigators, institutional review boards (IRBs), and any national health authorities where study is being considered.
- **Risk Minimization** by excluding high risk patients such as those with a history of RPOA, subchondral fractures, or joint dysplasia; minimizing the dose of anti-NGF treatment and excluding concomitant chronic NSAIDs. In non-OA indications, because of the apparent need for higher doses of anti-NGF, we would also exclude patients with evidence of mechanical/structural joint diseases.
- **Restricting Use to High Unmet Need Populations** until such time that the data support the study of additional populations. These include OA and non-OA pain patients (eg with cancer, neuropathic, thermal injury, or visceral pain conditions) demonstrated to have an insufficient response to standard of care; patients intolerant

to or with contraindications (absolute or relative) to standard of care; and patients awaiting TJR surgery (eg, with an anticipated wait of 3 to 9 months).

- **Demonstrating Efficacy in the Selected Populations** that is superior to other options available (eg, in patients with inadequate response to NSAIDs, demonstrating clinically meaningful superiority to NSAIDs).
- **Determining Long Term General Safety** of the potential long-term consequences of chronic NGF blockade (eg, on peripheral nerves, motor functioning, edema).
- **Defining Joint Safety Risks** that remain after instituting the risk minimization strategies above. This would include intention-to-treat (ITT) follow-up of all patients for the intended duration of the study to 6 months after the last planned dose and assessment of operative complications and outcomes in TJR cases.
- **Additional Risk Factor Characterization** by improving the baseline assessment of joint status and collecting data on potential prognostic indicators such as carboxy-terminal collagen crosslinks (CTX) biomarkers, imaging (eg, ultrasound to determine joint space dimensions), and actimetry to identify factors that might contribute to any residual risks of therapy with REGN475.
- **Risk Management** by discontinuing patients who develop sentinel findings such as subchondral fracture or accelerated joint space narrowing and having an independent data monitoring committee (IDMC) assess the emerging data to identify additional risk factors and recommend actions.

# REGULATORY HISTORY

A summary of the relevant regulatory history for the REGN475 clinical development program is provided in Table 1.

**Table 1: Relevant Regulatory History for REGN475 Clinical Development**

| Date | Description | Summary |
|---|---|---|
| 12/30/2008 | IND 103,245 submitted | To conduct Protocol R475-PN-0817 in Healthy Subjects |
| 02/2009 | Protocol R475-PN-0817 | Study initiation |
| 2009 – 2010 | Submitted Protocol R475-PN-0901 | Osteoarthritis of the knee |
| | Submitted Protocol R475-PN-0908 | Sciatic pain |
| | Submitted Protocol ACT11286 | Chronic pancreatitis pain |
| | Submitted Protocol ACT11308 | Vertebral fracture pain |
| | Submitted Protocol R475-PN-0909 | Thermal injury pain (subsequently terminated due to inability to enroll subjects) |
| 04/15/2010 | FDA requested information on cases of osteonecrosis and or rapidly progressive osteoarthritis (RPOA) in the REGN475 development program. | First contact from Division regarding safety signal. Regeneron confirmed no reports of osteonecrosis or RPOA. Provided details on 2 SAE reports of worsening arthritis in previously affected joints (R475-PN-0901). In May 2010, subsequently provided information on exposure, treatment assignment, case report forms. |
| 05/12/2010 | Email from FDA | Information requested and provided on two-subjects from R475-PN-0817 study |
| 06/22/2010 | Partial Clinical Hold of Pfizer's tanezumab program | Pfizer's OA program placed on hold |
| 07/29/2010 | Teleconference with FDA to discuss REGN475 program | Discussed nature of osteonecrosis/RPOA reports seen in tanezumab program. REGN475 program not on hold at this time. FDA requested that modifications be made to existing protocols Investigator's Brochure, informed consent form (ICF), safety monitoring and re-consent of patients. |
| 08/06/2010 | Submission of proposed modifications to clinical program as requested in 7/29/2010 teleconference | Included proposed modifications to ICF, Investigator's Brochure, exclusion criteria, patient monitoring, AE reporting, patient follow-up. |
| 11/02/2010 | FDA Advice Letter | Division's advice concerning the proposed modifications to clinical program submitted on 8/6/2010. |

**Table 1: Relevant Regulatory History for REGN475 Clinical Development (Continued)**

| Date | Description | Summary |
|---|---|---|
| 11/02/2010 | Discontinuation of Protocol ACT11308 (Vertebral Fracture) and ACT11286 (Chronic Pancreatitis) | Low patient recruitment and enrollment. Study ACT11286 subsequently terminated on 01/20/2011 and study ACT11308 on 01/31/2011. |
| 11/22/2010 | Investigator Communication | Provided Agency a copy of communicants sent to investigators regarding potential safety signal (as requested in Advice Letter received 11/2/2010). |
| 12/20/2010 | Submission provided response to Agency Advice Letter comments confirming changes to be made to clinical program | Provided updated Investigator's Brochure, Rev 3. Regeneron committed that "all reports of bone- and joint-related events will be coded as "unexpected" and "possibly related" unless there is a clear, alternative explanation for the event. |
| 12/23/2010 | FDA informed Regeneron via teleconference that that IND 103,245 was being placed on clinical hold. | Discussed additional report of pathologically confirmed osteonecrosis in a low-back pain trial with a second compound indicating safety signal may be a class effect. Division noted that an Advisory Committee would be convened. |
| 02/3/2011 | Teleconference with Division to discuss Regeneron participation in a public Advisory Committee meeting in late summer with other sponsors of anti-NGF products. | The purpose of the Advisory Committee is to discuss the potential toxicity of the class and if there is a path forward to continue work with anti-NGF products. |
| 2/18/2011 | Submission to provide copies of investigator and IRB communications regarding clinical hold and request for investigators to follow-up with study patients regarding joint related AEs. | Follow-up by investigators with subjects resulted in joint-related adverse event reports. The initial Medwatch reports, follow-up, and supporting information (case report forms, X-ray, pathology) were submitted to the Division as available between March and July 2011. |
| 07/28/2011 | Teleconference with FDA and other anti-NGF sponsors | Postponement of 9/13/2011 Advisory Committee meeting due large volume of information Division still needed to review. Advisory Committee meeting subsequently rescheduled for 03/12/12. |
| 12/5/2011 | Type A Meeting with FDA and other anti-NGF sponsors | Discussion with Division regarding the process for FDA independent adjudication and the timing and type of information to be presented at the upcoming Advisory Committee meeting. |
| 12/21/2011 | Submission of all REGN475 clinical study reports to Division | Studies which will be described in our briefing document/advisory committee presentation |

# 1. INTRODUCTION AND UNMET MEDICAL NEED

## 1.1. Introduction

Persistent pain represents a substantial and growing unmet medical need, affecting nearly half of all people seeking medical care in the United States. Persistent or inadequately treated pain has a profound impact on the quality of life (QOL) for millions of people worldwide. In addition, it is associated with a huge cost to society – as much as $635 billion in healthcare costs and lost productivity each year (Institute of Medicine Report Brief 2011).

While a wide variety of analgesic medications are currently available, many patients with acute and chronic pain still do not receive adequate relief or are unable to tolerate therapy. The limitations of currently available analgesic therapies are well-known and include central nervous system effects, nausea and vomiting, gastrointestinal (GI) bleeding and ulceration, constipation, hepatotoxicity, cardiovascular events, renal toxicity, and potential for abuse and dependence. In 1999 it was estimated that approximately 103,000 hospitalizations and 16,500 deaths occur yearly in the United States as a result of non-steroidal anti-inflammatory drug (NSAID) -related ulcer complications (Wolfe 1999).

Despite incremental advances in opioid-based or cyclooxygenase-based therapies, there has been little success in identifying and developing treatments based upon new targets that overcome the limitations of currently available chronic analgesic treatment. The targeting of nerve growth factor (NGF) – a neurotrophin that has been known for decades – is the first potential advance in pain management in many years. An effective anti-NGF therapy has the potential to help those patients who are unable to achieve adequate pain relief with existing therapies and/or who are unable to tolerate or are not good candidates for existing therapies.

## 1.2. REGN475

Over the past few years, Regeneron has been developing, in collaboration with Sanofi, REGN475. REGN475 is a fully human IgG4 monoclonal antibody (mAb) that specifically binds mature and proNGF with cross-reactivity to all mammalian NGFs tested (human, monkey, mouse, and rat NGF). REGN475 blocks NGF signaling through its tyrosine kinase type 1 (TrkA) and p75 receptors. REGN475 does not bind to or block signaling by other neurotrophins, notably neurotrophin-3 (NT-3), NT-4/5 or brain-derived neurotrophic factor. The development of REGN475 focused on patients with unmet needs for analgesia.

At the same time, Pfizer and Janssen were developing tanezumab and fulranumab, respectively. The US Food and Drug Administration (FDA) informed us that data from their development programs pointed to a risk of unexpected joint replacement in patients who had received treatment with an anti-NGF antibody. Moreover, these joint replacements seemed to be associated with pathology that was atypical for osteoarthritis (OA) and there was a question as to whether these occur in patients previously unknown to have OA. In light of these developments, the FDA placed our development program on hold, along with the Pfizer and Janssen programs.

Since that time, we have seen persuasive information from the Pfizer and Janssen anti-NGF development programs to support the conclusion that the clinical hold can be lifted. Their data

suggest hypotheses about measures that can be taken for risk minimization. These sponsors have proposed populations in which it might be appropriate to renew development even if there is some element of residual risk and we agree.

## 1.3. Burden Of Painful Conditions

There are many painful conditions that might be candidates for anti-NGF therapy. As of the date of this briefing book, publically available data indicate that anti-NGF agents have significant benefit in OA and chronic low back pain. Cancer pain is also being studied, and a variety of other painful conditions have been explored.

This briefing book will focus on OA and cancer pain. With respect to OA, there are 26 million Americans with OA. At this time, we do not believe that they are all candidates for an anti-NGF agent. We do not, at the current time, envision a general OA pain indication for REGN475. Instead, we are talking about only a subset of patients: patients with pain despite NSAID therapy, patients intolerant to NSAIDs, patients awaiting total joint replacement (TJR), and perhaps other subgroups. These OA subgroups present a particularly compelling unmet need, as do patients with cancer pain. Our development program will be designed to seek registration in those subsets of OA patients and other unmet medical need pain states by systematically and prospectively studying REGN475 to establish, in those patients, a positive benefit/risk ratio.

### 1.3.1. Osteoarthritis

Osteoarthritis is a progressive, chronic disease which is caused by the breakdown and loss of cartilage of the joints and which leads to pain in the hips, knees, hands, feet and spine. It is characterized by focal areas of loss of articular cartilage in synovial joints accompanied by subchondral bone changes, osteophyte formation at the joint margins, thickening of the joint capsule and mild synovitis. Symptoms and disability increase in prevalence with increasing age (Hawker 2001; Badley 1995) and people with OA use health-care services at a higher rate than a representative group of all adults (Gabriel 1997). The prevalence of OA in patients aged 65 and older is 60% in men and 70% in women, and continually rising.

Osteoarthritis has a major impact on functioning and independence and ranks among the top ten causes of disability worldwide (Badley 1991). The number of people with OA disability is expected to double by the year 2020 (Elders 2000), thereby increasing the already significant economic burden of OA (Gupta 2005). There is also a tangible emotional burden associated with OA. More than 40% of patients surveyed said OA has had a negative impact on their daily life, over 75% said OA limits their ability to perform daily activities, and more than 75% of those surveyed said that OA has had a negative impact on their physical health (Zaza and Baine 2002).

Non-steroidal anti-inflammatory drugs are the mainstay of treatment in patients with mild-to-moderate OA. Their efficacy is well-documented, but their use is not without risk (Wolfe 1999; Silverstein 2000; Makarowski 2002; Bjordal 2004; Jenkins and Seligman 2005; Bingham 2007). The risks associated with long-term therapy have been well-characterized and include GI bleeding and increased risk of cardiovascular events (Lanas 2010; Trelle 2011). In addition, patients must take these medications daily to maintain pain relief and this can result in patient dissatisfaction when their pain returns between doses.

In some patients, eg, those with hypertension and pre-existing renal or GI disease, the chronic use of NSAIDs may be relatively contraindicated. The availability of alternative treatment options with more effective analgesia and/or fewer or different associated side-effects that can be used in patients who cannot or should not take NSAIDs or opioids remains an unmet medical need.

Total hip arthroplasty and knee joint arthroplasty are generally accepted as reliable and appropriate surgical procedures to restore function and improve health-related QOL in patients with hip and knee OA who are not obtaining adequate pain relief and functional improvement with a combination of pharmacological and non-pharmacological treatments (Zhang 2008). In addition, it has also been demonstrated that patients with less pain and disability at the time of surgery will have better clinical outcomes (Nilsdotter 2003; Lingard 2004), supporting a role for better pain management prior to surgery. However, it is also important to remember that there are many patients who are unable to undergo these procedures because of medical limitations, and as such, would require pain management for longer periods of time.

### 1.3.2. Intractable Cancer Pain

Pain is one of the most common symptoms associated with cancer or its treatment. It occurs in approximately 30% of patients with newly-diagnosed cancer, 30%-50% of patients undergoing treatment, and 70%-90% of patients with advanced cancer, including those patients with metastatic bone disease (Portenoy & Lesage 1999).

Despite advances in pain management, there is evidence that the prevalence of inadequately treated cancer pain in patients with solid tumors ranges from 15% to more than 75%, depending upon the type and extent of disease (Portenoy 2011). Those who care for patients nearing the end of life advocate making these patients as comfortable and free of pain as possible. Yet, research indicates that many such patients are undertreated and thus suffer significant and unnecessary pain (Rolnick 2007; Cork 2003; Perron and Schonwetter 2001).

A major reason that cancer pain is often difficult to control is that the pain of cancer is generally not limited to a single site or mechanism. Thus, approaches such as targeted radiation or surgical excision may offer only limited relief. In addition, the pain medications most commonly used to treat cancer pain are often limited by side effects; titration to adequate dosing is often not achieved. Systemic therapy – ideally one without central nervous system effects – is an approach that might help alleviate pain in these difficult-to-treat cases.

## 1.4. Currently Available Treatments

### 1.4.1. Non-steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs provide pain relief and are indicated for use in OA pain. Many are also approved for a more general relief of pain indication and low doses of NSAIDs are approved for over-the-counter sale as analgesics. Not all patients get sufficient relief from NSAIDs at either the over-the-counter or prescription doses, and many patients are either not good candidates for NSAIDs (eg, due to difficult to manage hypertension, reduced renal function, history of upper GI ulcers, cardiovascular disease, or a myriad of other conditions) or are not able to tolerate some of the symptomatic side effects of full-dose NSAID therapy.

The use of NSAIDs in OA is based upon a large body of evidence and further supported by The American College of Rheumatology guidelines on management of OA, updated in 2000 (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines 2000) which recommended acetaminophen as first line pharmacological therapy for OA. This recommendation was subsequently modified in 2000 to suggest that 'for those patients who fail to obtain adequate symptomatic relief with acetaminophen, alternative or additional pharmacologic agents should be considered'. 'The choice of other agents should be made after evaluation of risk factors for serious upper GI and renal toxicity'.

#### 1.4.1.1. Efficacy of NSAIDs vs. Acetaminophen in Osteoarthritis

In 2006, a Cochrane Analysis of the efficacy and safety of acetaminophen and NSAIDs was published. Fifteen randomized, controlled trials (RCT's) involving 5986 participants were included in this review. Seven RCT's compared acetaminophen to placebo and 10 RCT's compared acetaminophen to NSAIDs. In the placebo-controlled RCT's, acetaminophen was superior to placebo in 5 of the 7 RCT's and had a similar safety profile. Compared to placebo, a pooled analysis of five trials of overall pain using multiple methods demonstrated a statistically significant reduction in pain, however the magnitude of pain reduction was deemed of questionable clinical significance (standard mean difference of -0.13, 95% CI -0.22 to -0.04). The relative percent improvement from baseline in the pooled analysis was 5% with an absolute change of 4 points on a 0 to 100 scale.

In the comparator-controlled RCTs, acetaminophen was less effective overall than NSAIDs in terms of pain reduction, global assessments and functional status. No significant difference was found overall between the safety of acetaminophen and NSAIDs, although patients taking traditional NSAIDs were more likely to experience an adverse GI event (RR 1.47, 95% CI 1.08 to 2.00). A total of 19% of patients in the traditional NSAID group versus 13% in the acetaminophen group experienced an adverse GI event. However, the median trial duration was only 6 weeks and it was difficult to assess adverse outcomes in this relatively short time period.

The authors concluded that NSAIDs are superior to acetaminophen for improving knee and hip pain in patients with OA, but that the analysis did not support long term use of NSAIDs for this condition. As serious adverse effects are associated with oral NSAIDs, only limited use of these agents was recommended (Towheed 2006).

#### 1.4.1.2. Safety of NSAIDs in Osteoarthritis

As noted previously, the limitations of NSAID use remain a concern for long-term therapy. These limitations include the risk of developing significant injury to the upper gastrointestinal (GI) tract (Gabriel 1991; Henry 1996). The annualized incidence rate of symptomatic GI ulcers and ulcer complications in NSAID users ranges from 2% to 4% (1%-2% for ulcer complications alone) (Gutthann 1997; Singh 1998). In 1999, NSAID-related ulcer complications were estimated to lead to 103,000 hospitalizations and 16,500 deaths yearly in the United States (Wolfe 1999).

Nonsteroidal anti-inflammatory drug labeling has long identified the risk of hypertension with NSAID use and of fluid retention in edema. These concerns limit the use of NSAIDs with hypertension or underlying heart disease. Nonsteroidal anti-inflammatory drug labeling notes the risk of renal effects; patients with underlying renal disease are poor candidates for NSAIDs.

Other risks associated with NSAIDs include elevated liver enzymes and hepatic reactions as well as serious skin reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis which can be fatal.

In 2004, rofecoxib, the selective COX-2 inhibitor, was voluntarily withdrawn from the market by its manufacturer after the results of a randomized placebo-controlled trial showed an increased risk of cardiovascular events associated with the drug (Bresalier 2005). This finding was reproduced in a trial of another selective COX-2 inhibitor, celecoxib (Solomon 2005). Since then, debate has surrounded the cardiovascular safety of all NSAIDs (Jenkins FDA Memo 2005, Kearney 2006). More recently, the Agency decided against the approval of etoricoxib and lumiracoxib because of concerns about risk/benefit.

## 1.4.2. Opioids

Opioids are potent analgesics that work primarily by targeting spinal and supraspinal opioid receptors, and reducing the flow of nociceptive transmission. In addition, cellular studies suggest that there are peripheral opioid receptors in inflamed osteoarthritic synovial tissue, which may also mediate analgesic effects (Stein 1996). Opioids have been shown to be effective in the treatment of OA (Avouac 2007; Markenson 2005). However, their use can be associated with both acute and chronic side effects. Acute risks include somnolence, nausea, constipation, motor effects, respiratory depression, and histamine release resulting in peripheral vasodilation as well as pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension. The chronic use of opioids also carries the risks of abuse, dependency and addiction. The American College of Rheumatology guidelines on management of OA, updated in 2000, suggests that opioids be used in OA only if management with NSAIDs is ineffective, intolerable, or otherwise contraindicated (American College of Rheumatology Subcommittee on Osteoarthritis Guidelines 2000). In addition, the utility of opioids in OA has also been questioned (Pergolizzi 2008; see below).

### 1.4.2.1. Evaluation of Opioids in Osteoarthritis

In 2009, a Cochrane Collaboration analysis was published of the efficacy and safety of opioids in OA of the knee and the hip. Ten trials with 2268 participants were included in the analysis which included treatment with oral codeine, transdermal fentanyl, oral morphine, oral oxycodone and oral oxymorphone.

Overall, opioids were more effective than control interventions in terms of pain relief (standardized mean difference -0.36, 95% CI -0.47 to -0.26) and improvement of function (standardized mean difference -0.33, 95% CI -0.45 to -0.21). Significant differences in effects according to type of opioid, analgesic potency (strong or weak), daily dose, duration of treatment or follow-up were not observed.

Adverse events were more frequent in patients receiving opioids compared to controls. Patients were 55% more likely to experience AEs in experimental groups compared to placebo (RR 1.55, 95% CI 1.41 to 1.70). The pooled risk ratio was 1.55 (95% CI 1.41 to 1.70) for any AE (4 trials), 4.05 (95% CI 3.06 to 5.38) for dropouts due to AEs (10 trials), and 3.35 (95% CI 0.83 to 13.56) for serious adverse events (SAEs) (2 trials). The number needed to harm to cause 1 additional patient to experience an AE, as compared to placebo, was 12 (95% CI 10 to 16). Results were consistent between different studies and different types of opioids (p for interaction = 0.95).

The authors concluded that there were small-to-moderate beneficial effects of non-tramadol opioids in the treatment of OA, but that these benefits were outweighed by a large increase in the risk of AEs. It was suggested that non-tramadol opioids should not be routinely used, even if osteoarthritic pain is severe (Nüesch 2010).

It is also important to note that many patients with OA can be older, and as such, may have compromised renal or hepatic function which can alter the clearance of opioid agents. In addition, many patients will also be taking multiple other medications secondary to co-morbid conditions, some of which can alter hepatic metabolism and also prolong opioid clearance.

A recent consensus statement about opioid use in the elderly (Pergolizzi 2008) points out that the tolerability profile of opioids is very important in elderly patients, as AEs, which have minimal consequences in younger patients, such as drowsiness, dizziness, GI tolerability and motor imbalance, can have serious consequences in older patients.

### 1.4.3. Tramadol

Tramadol is an atypical opioid agent because it activates both opioid receptors and descending inhibitory pain systems. Tramadol is increasingly used for the treatment of OA because it does not produce GI bleeding or renal problems and does not affect articular cartilage (Cepeda 2007). A number of studies have demonstrated that tramadol (Ultram®) reduces pain and improves function in patients with OA (Burch 2007; Malonne 2004; Adler 2002), but that these improvements are often associated with many of the AEs observed with other opioid agonists (e.g. nausea, vomiting, somnolence). In addition, a recent controlled study (DeLemos 2011), reported a significant improvement in the patient global assessment at the highest dose (300 mg qD), but no difference from placebo in either pain (numeric rating sale [NRS]) or function (Western Ontario and McMaster Osteoarthritis Index [WOMAC]) for all 3 doses studied (100, 200 and 300mg qD).

## 1.5. Proposed Basis for Removal of the Clinical Hold and Re-Initiation of Clinical Studies

Although there are effective analgesics for many patients with pain, these agents do not work for everybody and their use is associated with meaningful intolerability, morbidity and mortality. Thus, a possible risk associated with anti-NGF treatment needs to be placed in the context of the unmet clinical need and the known toxicities of existing therapies.

Our position at Regeneron and Sanofi is that the current data, while providing evidence for the efficacy of anti-NGF therapy, does not support anti-NGF therapy as a general treatment for OA or other pain conditions for which there are adequate treatments; the observed safety signals mentioned above need to be understood to a much greater degree before that could be the case. However, there may be a role for anti-NGF therapy in pain conditions where there is a high unmet need, ie, those for which there are no adequate alternatives. This is predicated on being able to demonstrate a clinically significant benefit over existing options and an acceptable safety profile such that a positive benefit/risk can be established within this context.

For REGN475, we propose a path forward implementing the following strategies:

- **Informed Consent** of patients and appropriate communication of the data and potential risks to investigators, institutional review boards (IRBs), and any national health authorities where study is being considered.
- **Risk Minimization** by excluding high risk patients such as those with a history of rapidly progressive osteoarthritis (RPOA), subchondral fractures, or joint dysplasia; minimizing the dose of anti-NGF treatment and excluding concomitant chronic NSAIDs. In non-OA indications, because of the apparent need for higher doses of anti-NGF, we would also exclude patients with evidence of mechanical/structural joint diseases.
- **Restricting Use to High Unmet Need Populations** until such time that the data support the study of additional populations. These include OA and non-OA pain patients (e.g. with cancer, neuropathic, thermal injury, or visceral pain conditions) demonstrated to have an insufficient response to standard of care; patients intolerant to or with contraindications (absolute or relative) to standard of care; and patients awaiting TJR surgery (for example, with an anticipated wait of 3 to 9 months).
- **Demonstrating Efficacy in the Selected Populations** that is superior to other options available (eg, in patients with inadequate response to NSAIDs, demonstrating clinically meaningful superiority to NSAIDs).
- **Determining Long-Term General Safety** of the potential long-term consequences of chronic NGF blockade (eg, on peripheral nerves, motor functioning, edema).
- **Defining Joint Safety Risks** that remain after instituting the risk minimization strategies above. This would include intention-to-treat (ITT) follow-up of all patients for the intended duration of the study to 6 months after the last planned dose and assessment of operative complications and outcomes in TJR cases.
- **Additional Risk Factor Characterization** by improving the baseline assessment of joint status and collecting data on potential prognostic indicators such as carboxy-terminal collagen crosslinks (CTX) biomarkers, imaging (eg, ultrasound to determine joint space dimensions), and actimetry to identify factors that might contribute to any residual risks of therapy with REGN475.
- **Risk Management** by discontinuing patients who develop sentinel findings such as subchondral fracture or accelerated joint space narrowing, and having an independent data monitoring committee (IDMC) assess the emerging data to identify additional risk factors and recommend actions.

These concepts are discussed in greater detail in Section 5.

# 2. PRECLINICAL DEVELOPMENT OF REGN475

## 2.1. Pharmacology

### 2.1.1. Overview of NGF and the Other Neurotrophins

Neurotrophins are a family of protein growth factors that play a role in the development, differentiation, survival and death of neuronal and non-neuronal cells (Chao 2006). The first neurotrophin to be identified was NGF, and its role in the development and survival of both peripheral and central neurons in the developing nervous system has been well characterized (Smeyne 1994; Crowley 1994). However, in the normal adult, NGF is not required as a survival factor but acts as a pain mediator that sensitizes neurons (Pezet and McMahon 2006).

Nerve growth factor activity is mediated through 2 different membrane-bound receptors, the high-affinity neurotrophic TrkA receptor and the low-affinity p75 common neurotrophin receptor. The NGF/TrkA system appears to play a major role in the control of inflammation and pain, and is upstream of several relevant molecular pathways.

Administration of NGF has been shown to provoke pain in both rodents (Lewin 1994) and humans (McArthur 2000), while NGF antagonists have been shown to prevent hyperalgesia and allodynia in animal models of neuropathic and chronic inflammatory pain (Ramer 1999). Humans with mutations in TrkA (HSAN IV) or NGF (HSAN V) have been shown to experience a loss of deep pain perception (Indo 1996; Einarsdottir 2004). In addition, NGF is known to be elevated in the synovial fluid of patients suffering from rheumatoid arthritis and other types of arthritis (Aloe 1992), and to be up-regulated in injured and inflamed tissues in conditions such as cystitis, prostatitis, and chronic headache.

In 2006, Hefti *et.al.* suggested that the blockade of NGF in the adult human could be a highly effective therapeutic approach for many pain states (Hefti 2006). This has subsequently been confirmed in several clinical studies in OA (Lane 2010, Tiseo 2010; Sanga 2011; Ekman 2011), and in a single study in chronic lower back pain (Katz 2011). As noted above, the expression of NGF is high in injured and inflamed tissues, and activation of the NGF receptor TrkA on nociceptive neurons triggers and potentiates pain signaling by multiple mechanisms. Inhibition of NGF function and signaling blocks pain sensation as effectively as cyclooxygenase inhibitors and opiates in rodent models of pain.

REGN475 is a fully-human high-affinity mAb directed against NGF. By selectively blocking NGF, REGN475 has the potential to be effective without the adverse side effects of traditional, less specific analgesic medications.

### 2.1.2. In Vitro Pharmacology

REGN475 binds with high affinity to both the mature and pro-forms of human NGF, as well as to mouse and rat NGF. In addition, the amino acid sequences of human and monkey NGF are identical. Therefore, monkey, rat, and mouse are all relevant species for toxicology and nonclinical studies.

REGN475 is specific for NGF, and does not detectably bind any other members of the neurotrophin family, which includes brain-derived neurotrophic factor, NT-3, and NT-4/5.

REGN475 potently blocks NGF signaling by preventing the interaction of NGF with its receptors, TrkA and p75. Neurotrophin TrkA receptor contains a tyrosine kinase cytoplasmic domain, which is activated upon NGF-induced receptor dimerization and mediates much of the bioactivity of mature NGF. The low-affinity neurotrophin receptor p75 can also modulate the interaction of NGF with TrkA.

### 2.1.3. Evaluation of the Efficacy and Joint Safety of REGN475 in a Mouse Medial Meniscus Destabilization Model of Osteoarthritis

The aim of this study was to determine the efficacy and safety of treatment with REGN475 in a preclinical model of OA. Bi-weekly administration of the REGN475 anti-NGF antibody did not significantly reduce the tactile allodynia observed after surgical destabilization of the medial meniscus (DMM) in mice. Administration of REGN475 also did not result in any statistically significant anatomical differences in a variety of bone, vascular, and nerve markers, suggesting that REGN475 can be safely administered in these models. In addition, animals administered REGN475 showed no adverse impact in general activity as assessed by open field behavior. Although our findings do not suggest efficacy of REGN475 in the management of tactile allodynic pain in this OA model, initial human clinical studies have suggested efficacy of this antibody against the pain reported by human OA patients. Our data suggest that REGN475 does not cause any notable anatomical pathology of the bone, vasculature, or nerves in the OA-like joint.

#### 2.1.3.1. Test System

The study described in this report uses surgical destabilization of the mouse medial meniscus to evaluate the effects of anti-NGF antibodies in a model of OA. In this model, the medial meniscus of one knee is destabilized, which leads to morphological changes reminiscent of the osteoarthritic joint within 8 weeks (Moodie 2011). Specifically, tibial bone alterations are pronounced by microCT scanning, and are characterized by posterior subchondral bone loss and anterior compensatory bone growth. Cartilage loss also occurs, and is more marked in the region of the posterior tibia where bone loss is observed. Behaviorally, animals show a progressive mechanical (tactile) allodynia that is opiate-responsive (Malfait 2010). In the current experiment, animals were behaviorally tested for 16 weeks after medial meniscus destabilization, and were then sacrificed for radiological and histological evaluation of the knee. During the 16-week period, animals developed statistically significant tactile allodynia, increased bone volume, and increased bone mineral content in the injured knee.

#### 2.1.3.2. Experimental Design

C57Bl/6 mice obtained from The Jackson Laboratories (Bar Harbor, ME) were pseudo-randomly assigned to 1 of 4 treatment groups (n=10-14 per group). The medial meniscus of the left knee was destabilized by transection in 3 of the groups (the DMM groups), while the fourth group received all surgical procedures with the exception of the actual destabilization (the sham group). One of the 3 DMM groups served as the experimental group and was treated with 50 mg/kg REGN475 every 2 weeks starting 24 hours after surgery. The other 2 DMM groups served as controls for treatment. The first was a vehicle control group that received an injection of phosphate-buffered saline (PBS) in the same volume and dosing regimen as the REGN475 treatment group. The second treatment control group received 50 mg/kg of REGN646, an IgG

isotype control, in the same volume and dosing regimen as the REGN475 treatment group. The final group of animals, which had received the sham surgery rather than the medial meniscus destabilization, received injections of PBS control in the same volume and dosing regimen as the other groups. Animals were evaluated for tactile mechanical allodynia using von Frey hairs (graded nylon monofilaments). Each hair is designed to apply a different maximal pressure when applied, until it bends, to the plantar surface of the hind paw of the affected limb. The up-down method of serial pressures was used to estimate the pressure paw withdrawal threshold for each animal in grams. Von Frey hair testing was conducted before animals received their surgical procedure (baseline measurement) and every 2 weeks starting 2 weeks after their surgical procedure. Mechanical allodynia is a feature of human OA, although perhaps not the primary pain complaint (eg, see Imamura 2008). In addition, animals were evaluated for general activity on the prickly floor open field for one hour. Animals were euthanized 16 weeks after the surgical procedure, and blood was collected for assessment of antibody levels. In addition, knees were collected from all animals and prepared for histological evaluation. Half of the knees were immersion-fixed for microCT scanning to assess bone volume, bone mineral content, and bone density before being processed histologically and stained with safranin O/fast green to evaluate cartilage. The other halves of the knees were fresh frozen for immunohistochemical staining of vasculature (anti-CD-146) and nerves (anti-tyrosine hydroxylase for sympathetic nerves and anti-PGP9.5 for sensory nerves). Densitometric and stereological procedures were used for the evaluation of cartilage, vasculature, and nerve terminals.

Results from all measures were analyzed using analyses of variance (ANOVA) followed by Tukey post-hoc tests when the initial ANOVA achieved statistical significance. In post-hoc analyses, significant effects of DMM were assessed by comparing sham-PBS animals to DMM-PBS animals. Significant effects of REGN475 treatment were assessed by comparing REGN475-treated DMM animals to REGN646 isotype control-treated DMM animals. For all analyses, statistical significance was determined at the 0.05 alpha level.

#### 2.1.3.3. Results

*General Health*

There were no statistically significant differences between the experimental groups in either body weight (data not shown), or in open field behavior (data not shown), suggesting that repeated dosing with REGN475 caused no adverse effect on overall animal health.

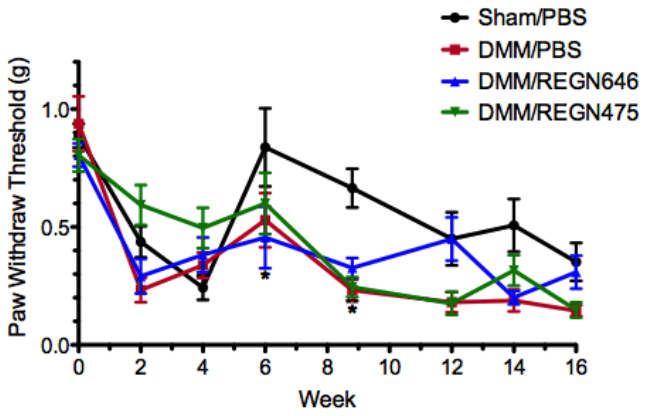
*Antibody Levels*

Blood was collected at the end of the experiment and enzyme-linked immunosorbent assays were conducted to measure plasma levels of REGN475. Circulating levels of REGN475 were similar to those of the control antibody REGN646, and were within concentrations previously observed to be efficacious (400-600 μg/ml, *data not shown*). Plasma was also assayed for the presence of mouse anti-human antibodies to rule out the possibility that animals had formed antibodies against the drug. No detectable levels of mouse anti-human antibodies were detected (data not shown).

*Nociceptive Behaviors*

The DMM surgery produced a statistically significant tactile allodynia as assessed with von Frey hairs. REGN475, however, produced no statistically significant relief of tactile allodynia in this model (see Figure 1).

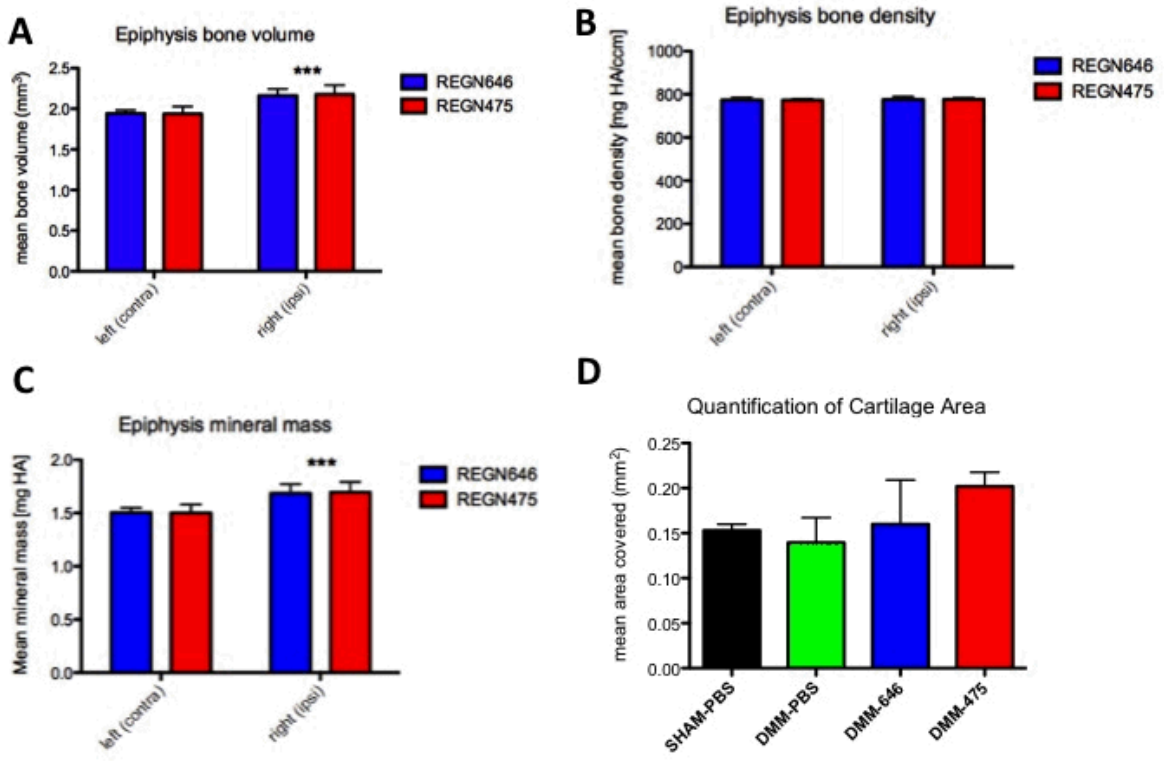
**Figure 1: Nociceptive Behavior following REGN475 Treatment in the DMM Model.**




*Bone and Cartilage*

The DMM surgery produced statistically significant increases in epiphysis bone volume and bone mineral mass without significantly impacting bone density or cartilage area. REGN475 produced no significant alterations in microCT bone volume (Figure 2A), microCT bone density (Figure 2B), microCT bone mineral mass (Figure 2C), or cartilage area (Figure 2D) relative to animals treated with the REGN646 control antibody.

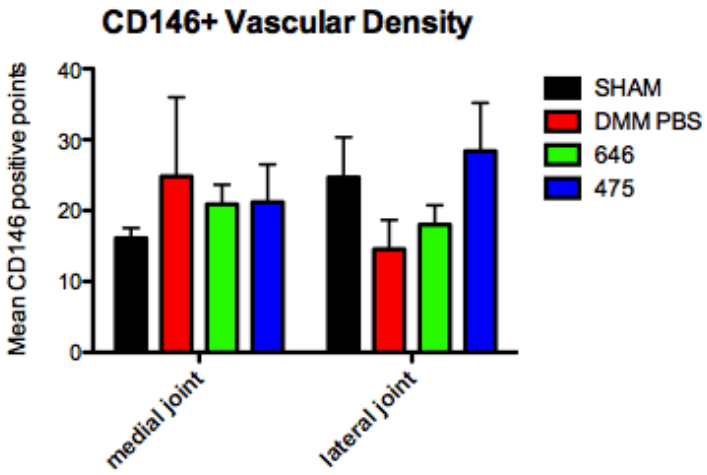
**Figure 2: Effect of REGN475 Treatment on Bone and Cartilage**




*Vasculature*

The DMM surgery produced no statistically significant alterations in knee joint vascular density, as assessed by point-count stereology in CD146-immunostained knee sections. REGN475 produced no statistically significant alterations in vascular density relative to its isotype control antibody, REGN646 (Figure 3).

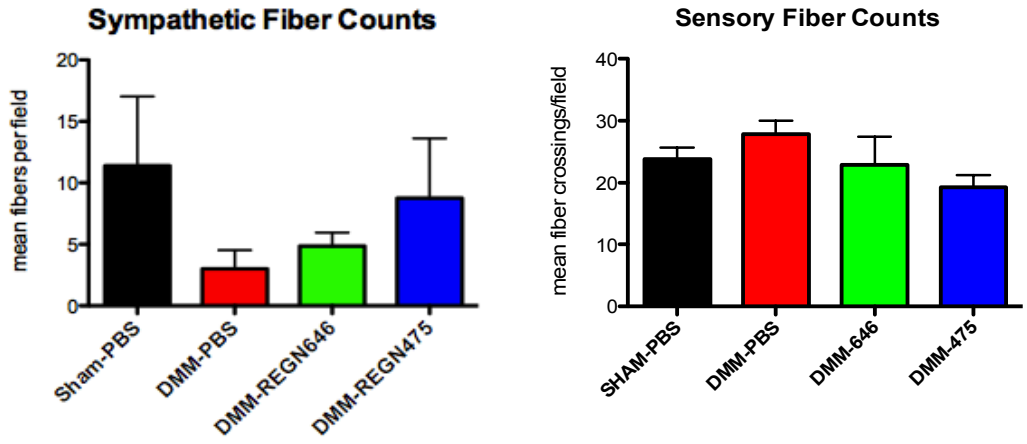
**Figure 3: Effect of REGN475 Treatment on Vascular Density**



*Innervation*

Alterations in sympathetic and sensory fiber counts as a result of the DMM surgery did not achieve statistical significance, although there was a tendency toward decreased sympathetic fiber counts in the PBS and REGN646-treated DMM groups that was partially prevented by REGN475 treatment. In addition, REGN475 produced no statistically significant alterations in sympathetic or sensory nerve fiber counts relative to its isotype control antibody, REGN646 (Figure 4).

**Figure 4: Effect of REGN475 Treatment on Nerve Fiber Counts**




### 2.1.3.4. Conclusion

This preclinical study demonstrated that REGN475 is not efficacious against the tactile allodynia induced in a medial meniscus destabilization model of OA. REGN475 also does not induce any statistically significant alterations in the bone, vascular, and nerve parameters evaluated in this study. Indeed, the DMM manipulation resulted in a slight decrease in vascular and sympathetic fiber density that, if anything, REGN475 improved (albeit not significantly). In addition, animals appeared grossly normal, with little attenuated weight gain and normal general activity in the automated open field. Animals achieved blood levels of antibody that have been associated with efficacious effects in previous pre-clinical animal models without showing evidence of mouse anti-human antibodies after 16 weeks of treatment.

While these data suggest that REGN475 is not efficacious against the tactile allodynia resulting from the DMM surgery, anti-NGF antibodies, including REGN475, have already been shown to be efficacious against the pain reported in human OA. The reason for failure to observe efficacy of REGN475 against allodynia in our model is currently unclear. One possibility, which is supported by recent publications (for review, see Mogil 2009), is that the type of pain commonly measured in animal OA models is not reflective of the type of pain evaluated by human OA patients when judging their level of suffering. That is, efficacy in one measure of pain does not necessarily translate to efficacy in others. A second possibility, however, is that animal models of arthritis fail to accurately emulate all aspects of human OA. Given this possibility, one cannot

be certain that the safety of REGN475 in the DMM animal model assures its safety in human OA patients. Nevertheless, its safety in the animal model is somewhat reassuring, because it suggests that the use of REGN475 in the context of a damaged joint does not meaningfully alter bone, vasculature density, sensory nerve density, sympathetic nerve density, or general behavior. Indeed, any trends observed in the data, particularly with regard to vascular density and sympathetic fiber density, suggest that REGN475 alleviates, rather than exacerbates, any detrimental impact of disease on these parameters.

### 2.1.4. Post-Operative Pain Model

A rodent model of post-operative incisional pain was used to demonstrate the analgesic efficacy of REGN475. Anesthetized C57BL/6 male mice received a hind paw incision through skin, fascia, and the underlying flexor muscle. Following the surgery, mice were studied for up to 3 days for tactile mechanical allodynia (using the von Frey Test) and thermal hyperalgesia (using the Hargreaves' Test). One day after surgery, animals were tested to confirm the presence of mechanical allodynia and thermal hyperalgesia. Immediately after testing, REGN475 or an isotype control IgG was administered by intravenous (IV) bolus. Pain behaviors were then tested for 2 days after antibody administration. REGN475 significantly reduced both mechanical allodynia and thermal hyperalgesia, suggesting efficacy against post-operative incisional pain (Figure 5).

**Figure 5: Effect of REGN475 on Mechanical Allodynia (von Frey Test) and Thermal Hyperalgesia (Hargreaves' Test) in a Post-Operative Incisional Pain Model**

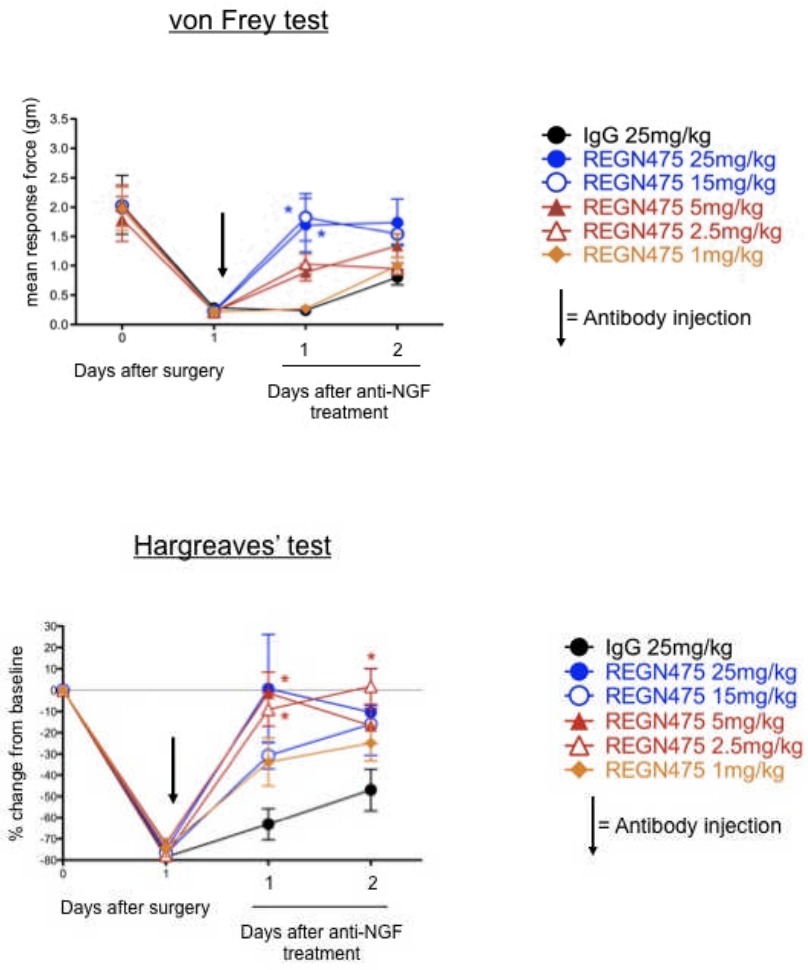



**Figure Legend:** *A single dose of antibody was administered via IV injection to C57BL/6 mice 1 day after surgery. REGN475 was administered at multiple doses (1, 2.5, 5, 15 or 25 mg/kg). Control IgG was administered at a single dose (25 mg/kg). There were n=7 per group, except for the IgG control group which had n=5. * p<0.05 vs. control IgG group*

REGN475 significantly alleviated post-operative mechanical allodynia at doses of 15 mg/kg and 25 mg/kg. Reduction in thermal hyperalgesia was even more striking, with significant efficacy observed at doses as low as 2.5 mg/kg. It is likely that REGN475's analgesic effects are specific to pathological pain, because separate experiments demonstrated that REGN475 does not alter baseline thermal nociception, even at doses as high as 100 mg/kg. In addition, efficacious doses of REGN475 do not induce non-specific behavioral toxicity, as evidenced by separate experiments showing that rotarod performance was unaffected by REGN475 at all doses tested (highest dose was 100 mg/kg).

### 2.1.5. Neuropathic Pain Model

Injury to a peripheral nerve in humans often results in persistent neuropathic pain that is characterized by a painful burning sensation, mechanical allodynia, and thermal hyperalgesia. The efficacy of REGN475 against neuropathic pain was tested in a commonly used animal model of nerve injury-induced pain, the partial sciatic nerve ligation model (also known as the Seltzer model).

After baseline nociceptive testing, adult male C57BL/6 mice were anesthetized and their sciatic nerves were surgically isolated. A suture was tightly ligated around the dorsal 1/3-1/2 of the sciatic nerve, a manipulation that consistently produced a long-lasting painful neuropathy. Seven days after surgery, mice were tested for both tactile mechanical allodynia (using the von Frey Test) and for thermal hyperalgesia (using the Hargreaves' Test) to verify successful ligation. Mice were then injected subcutaneously (SC) with 50 mg/kg REGN475 or isotype control antibody at either day 7 or 14 after surgery. Animals were retested for allodynia and thermal hyperalgesia every few days for approximately 1 month (Figure 6).

REGN475 produced a statistically significant reversal of mechanical allodynia and thermal hyperalgesia when administered either 7 or 14 days following partial sciatic nerve ligation. These data demonstrate that REGN475 is effective at reducing pain induced by a chronic nerve injury even after the pain is already well-established.

**Figure 6: Effect of REGN475 on Mechanical Allodynia and Thermal Hyperalgesia in a Partial Sciatic Nerve Ligation Model of Neuropathic Pain**

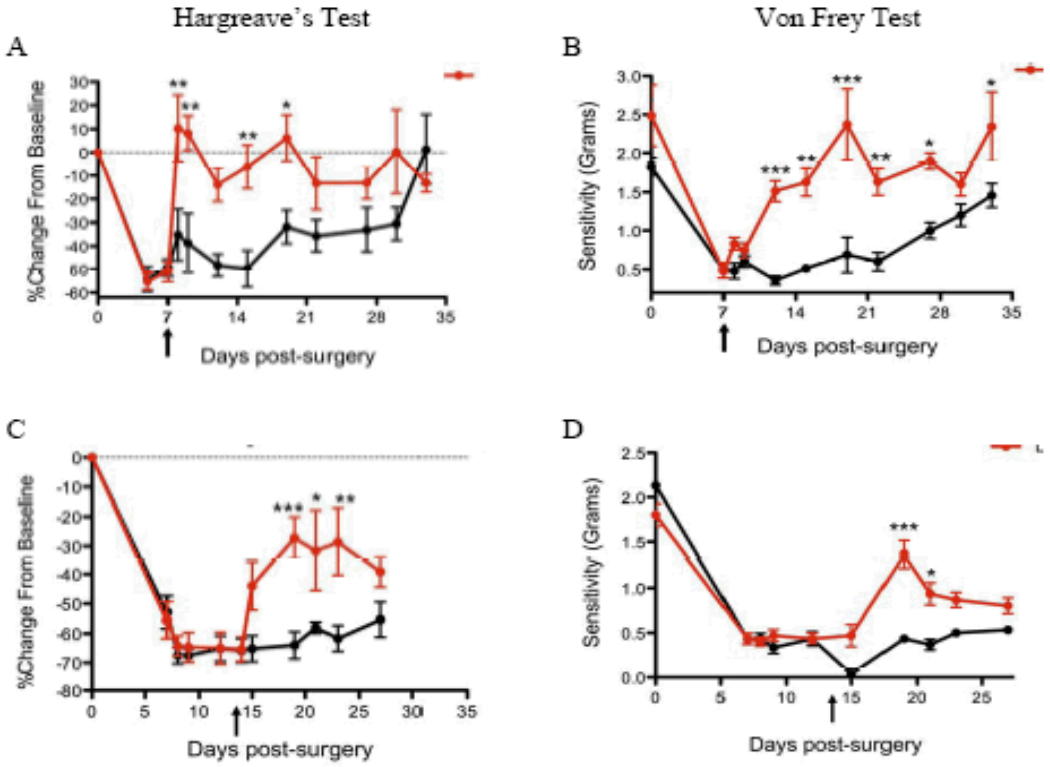



**Figure Legend:** *Mice (n=7 per group) were tested in the von Frey Test for mechanical allodynia (panels B & D) and the Hargreaves' Test for thermal hyperalgesia (panels A & C) prior to surgical intervention and every few days afterwards. REGN475 (red) or isotype control antibody (black) were administered SC at 50 mg/kg on day 7 (panels A & B) or day 14 (panels C & D) following surgery (antibody injection day indicated by arrow). Asterisks indicate time points at which animals treated with REGN475 show significantly different nociceptive responses than animals treated with control antibody, *p<.05, **p<.01, ***p<.001 by Bonferroni post hoc tests*

## 2.2. Pharmacokinetics

REGN475 pharmacokinetics (PK) was examined in both rats and cynomolgus monkeys following a single SC or IV injection at multiple dose levels.

The PK of REGN475 is similar between rats and monkeys. In both species, REGN475 exhibited linear PK; there were dose proportionate increases in both $C_{max}$ and area under the curve (AUC) estimates. In addition, the terminal half-life ($t_{1/2}$) of the injected material was long, ie, greater than 130 hours in rat and greater than 270 hours in monkey, and target-mediated clearance was not observed. Bioavailability of REGN475 was greater than 82%, regardless of species. There was no apparent difference between males and females, regardless of species.

## 2.3. Toxicology

A description of the toxicology studies conducted with REGN475 is summarized (Table 2) and described in further detail in the following paragraphs.

**Table 2: Summary of REGN475 Toxicology Studies**

| Study Type and Duration | Route of Administration | Doses | Primary Test Article Related Findings |
|---|---|---|---|
| | | | |
| A 5-Week (Every Other Week) Intravenous Infusion Toxicity and Toxicokinetic Study of REGN475 with an 8-Week Recovery Period in Sprague-Dawley Rats | 30-Minute Intravenous Infusion | 0, 0.5, 3, 15, 50 (mg/kg) | Moist alopecia in the ventral region of the neck with histological correlates related to inflammation<br>NOAEL: 3 mg/kg |
| A 5 Week (Every Other Week) Intravenous Infusion Toxicity and Toxicokinetic Study of REGN475 with an 8-Week Recovery Period in Cynomolgus Monkeys | 30-Minute Intravenous Infusion | 0, 0.5, 3, 15, 50 (mg/kg) | None<br>NOAEL: 50 mg/kg |
| A 13-Week (Every Other Week) Intravenous Infusion Toxicity and Toxicokinetic Study of REGN475 with a 13-Week Recovery Period in Cynomolgus Monkeys | 30-Minute Intravenous Infusion | 0, 0.5, 3, 15, 50 (mg/kg) | None<br>NOAEL: 50 mg/kg |
| A 13-Week (Every Other Week) Subcutaneous Toxicity and Toxicokinetic Study of REGN475 with a 13-Week Recovery Period in Cynomolgus Monkeys | Intrascapular Subcutaneous Injection | 0, 0.5, 3, 15, 50 (mg/kg) | None<br>NOAEL: 50 mg/kg |
| SAR164877 (REGN475): Intravenous Embryo-Fetal Toxicity Study in Rats | 30-Minute Intravenous Infusion | 0, 10, 50, 100 (mg/kg) | None<br>NOAEL: 100 mg/kg |
| Cross-Reactivity Study of Biotin REGN475 with normal Human, Cynomolgus Monkey, and Sprague-Dawley Rat Tissues (GLP) | In Vitro | 2, 30 (mcg/mL) | NA |

### 2.3.1. Repeat-dose Toxicity

Repeat-dose toxicology studies were conducted in 2 species, Sprague-Dawley rats and cynomolgus monkeys. These included a Good Laboratory Practice (GLP) 5-week repeat-dose study in cynomolgus monkeys followed by an 8-week recovery period, and a GLP 5-week repeat-dose study in rats followed by an 8-week recovery period. Both studies examined the effects of REGN475 following dosing every other week at doses up to 50 mg/kg. Toxicokinetic analyses indicated substantial blood levels of REGN475 that increased with dose, and that

anti-drug antibody formation was not a factor in either study. In addition, 13-week repeat-dose toxicity studies followed by a 13-week recovery period were conducted in cynomolgus monkeys at the same dose levels using the IV and SC routes. Embryo-fetal development was also evaluated in rats given 2 IV doses of REGN475 up to 100 mg/kg between gestation days 6 and 13; placental transfer was exhibited with REGN475. None of these studies demonstrated any direct findings due to REGN475 treatment and no osteoarthritic or vascular changes to bone were observed in any study.

#### 2.3.1.1. 5-Week Repeat Dose Toxicology Study in Rats

The primary REGN475-related finding in the rat study was moist alopecia that consisted of a patch of missing hair, primarily on the ventral region of the neck that progressed to a scabbing of the skin in all test article-treated groups. The frequency and severity of the alopecia correlated with increasing dose of REGN475. The observed skin lesions correlated with histopathologic findings of ulceration (mild-to-severe), chronic inflammation (mild-to-severe), and epithelial hyperplasia (minimal-to-severe). There was evidence of reversibility of the alopecia and histological correlates during recovery. Moist alopecia/scabbing was not considered to be a direct effect of REGN475 toxicity (more likely due to an altered perception of pain which results in a mechanical trauma related to repeated scratching of the area). Skin samples examined from other anatomic regions were unaffected, further suggesting that skin is not a target lesion. Bone tissue (sternum as well as the femorotibial joint) was evaluated histopathologically and did not reveal any test article-related changes.

#### 2.3.1.2. 5-Week Repeat Dose Toxicology Study in Cynomolgus Monkeys

There were no test article-related effects found during in-life evaluations, including a functional observational battery. REGN475 did not cause any significant changes in any clinical-pathology parameters. Post-mortem gross and histopathology evaluations did not reveal any test article-related findings. There were no anti-drug antibodies detected in any of the monkeys. Bone tissue (sternum as well as femur with a portion of the cartilaginous articular surface of the knee joint) was evaluated histopathologically and did not show any test article-related changes.

#### 2.3.1.3. 13-Week Repeat Dose IV Toxicology Study in Cynomolgus Monkeys

REGN475 did not cause any significant changes in any clinical-pathology parameters. Post-mortem gross and histopathology evaluations did not reveal any test article-related findings. Bone tissue (sternum as well as femur with a portion of the cartilaginous articular surface of knee joint) was evaluated histopathologically and did not show any test article-related changes.

#### 2.3.1.4. 13-Week Repeat Dose SC Toxicology Study in Cynomolgus Monkeys

There were no test article-related effects found during in-life evaluations, including a functional observational battery. REGN475 did not cause any significant changes in any clinical-pathology parameters. Post-mortem gross and histopathology evaluations did not reveal any test article-related findings. Bone tissue (sternum as well as femur with a portion of the cartilaginous articular surface of knee joint) was evaluated histopathologically and did not show any test article-related changes.

### 2.3.1.5. Embryo-Fetal Development Toxicology Study

Embryo-fetal development effects of REGN475 have been evaluated in a rat Segment II study. Pregnant dams (n = 35 per group) received two 10, 50 or 100 mg/kg IV doses of REGN475 during the 2-week period in which the organogenesis phase of pregnancy occurs (gestation days 6 and 13).

REGN475 exhibited placental transfer as significant REGN475 levels were found in fetal blood. All fetuses were evaluated on gestation day 21; there was no evidence of any fetal loss, organ malformations, or differences in fetal weight or mortality in animals treated with REGN475 when compared to animals treated with placebo. Evaluation of the fetuses' skeletal morphology did not reveal any test article-related effects on bone development.

# 3. OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

Following an evaluation of the safety and tolerability of the antibody in an ascending-dose, first-in-human (FIH) study, several pain indications were targeted for proof-of-concept evaluation in Phase 2. These indications included pain from OA of the knee, pain due to sciatica, pain of chronic pancreatitis and pain from vertebral fracture. A second Phase 1 study to evaluate the safety and tolerability of a new formulation of the drug was also conducted (TDU11480).

The FIH, OA and sciatica studies were completed and summary information is provided below. The chronic pancreatitis and vertebral fracture studies were closed early as a result of poor patient enrollment before the Clinical Hold. Patients were enrolled in the chronic pancreatitis and the vertebral fracture studies at the time of their termination and summary safety data for these studies is provided.

## 3.1. Phase 1 Study in Healthy Volunteers R475-PN-0817

**Study Title:** A Randomized, Double-Blind, Placebo-Controlled, Single-Dose Study of the Safety and Tolerability of REGN475 in Healthy Subjects.

### 3.1.1. Study Design Overview

This was an ascending, single-dose study in normal healthy volunteers. It included dose levels of 0.03, 0.1, 0.3, and 1.0 mg/kg administered IV and 0.1 and 0.3 mg/kg administered SC. Of the 56 subjects randomized and treated, 30 received REGN475 using an IV route of administration, 12 received REGN475 using an SC route of administration, and 14 received placebo (either IV or SC). Subjects were followed for 16 weeks following drug administration.

### 3.1.2. Study Population

Male or female volunteers, in general good health and between the ages of 21 to 65, who were able and willing to provide written informed consent and to follow study instructions.

### 3.1.3. Study Objectives

To evaluate the safety and PK of a single dose of REGN475 in healthy volunteers.

### 3.1.4. Results

Two subjects, 1 treated with placebo and 1 treated with REGN475 1.0 mg/kg IV, were lost to follow-up and did not complete the study. All other subjects completed the study.

Of note, during the dose ascension, several neurosensory and neuromuscular events were observed in the 1.0 mg/kg cohort. As a result, the decision was made not to enroll a 3.0 mg/kg cohort in this study conducted in healthy volunteers.

The observed increase in neurosensory and neuromuscular AEs in the 1 mg/kg IV dose cohorts suggested that doses lower than 1 mg/kg would need to be evaluated in the Phase 2 development program.

### 3.1.4.1. Treatment Emergent Adverse Events

A summary of the treatment-emergent adverse events (TEAEs) observed in this study is presented in Table 3. The safety analysis set (SAF), which includes all patients who received a dose of study medication analyzed "as treated", was used for all safety analyses.

The most common TEAE reported in the overall study was Arthralgia in 8/42 (19.0%) of REGN475-treated subjects and 1/14 (7.1%) of placebo-treated subjects (Table 4).

Several neurosensory and neuromuscular events were observed in the 1.0 mg/kg cohort. The first 6 subjects enrolled in this cohort reported 5 events: 2 events of Dysesthesia (related) and 1 event each of Hyperaesthesia (unrelated), Hypoaesthesia (related), and Arthralgia (related). Although no dose-limiting toxicities occurred in this cohort, the 1.0 mg/kg cohort was repeated as a result of these events. The repeat cohort had a similar AE profile including 5 reports of Arthralgia, 1 report of Dysesthesia, 1 report of Itching, and 1 report of Numbness in Hand. All AEs were considered related to study drug, and all were mild except for 1 instance of Arthralgia that was moderate in severity.

**Table 3: Summary of Treatment-Emergent Adverse Events (SAF) – R475-PN-0817**

| | | REGN475 | | | | | |
|---|---|---|---|---|---|---|---|
| **MedDRA System Organ Class (SOC) Preferred Term (PT)** [a] | **Placebo (n=14)** | **0.03 mg/kg IV (n=6)** | **0.1 mg/kg IV (n=6)** | **0.3 mg/kg IV (n=6)** | **1.0 mg/kg IV (n=12)** | **0.1 mg/kg SC (n=6)** | **0.3 mg/kg SC (n=6)** |
| Number of TEAEs: | 19 | 2 | 14 | 9 | 35 | 12 | 22 |
| Subjects with no TEAEs | 3(21.4%) | 2(33.3%) | 4(66.7%) | 2(33.3%) | 1(8.3%) | 1(16.7%) | 1(16.7%) |
| Subjects with at least one TEAE | 11 (78.6%) | 4(66.7%) | 2(33.3%) | 4(66.7%) | 11 (91.7%) | 5(83.3%) | 5(83.3%) |
| Subjects with study drug related TEAEs | 0 | 0 | 0 | 0 | 10 (83.3%) | 1(16.7%) | 2(33.3%) |
| Subjects with serious TEAEs | 0 | 0 | 0 | 0 | 0 | 0 | 1(16.7%) |
| Subjects with TEAEs resulting in discontinuation | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Subjects who died due to TEAE | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

[a] MedDRA (Version 11.1) coding dictionary was applied.

**Table 4: Summary of TEAEs Occurring in 2 or More Patients in the Combined REGN475 Group by Preferred Term (SAF) – R475-PN-0817**

| | | REGN475 | | | | | |
|---|---|---|---|---|---|---|---|
| **Preferred Term (PT)** [a] | **Placebo (n=14) n (%)** | **0.03 mg/kg IV (n=6) n (%)** | **0.1 mg/kg IV (n=6) n (%)** | **0.3 mg/kg IV (n=6) n (%)** | **1.0 mg/kg IV (n=12) n (%)** | **0.1 mg/kg SC (n=6) n (%)** | **0.3 mg/kg SC (n=6) n (%)** |
| Patients with at least one adverse event | 11 (78.6%) | 4 (66.7%) | 2 (33.3%) | 4 (66.7%) | 11 (91.7%) | 5 (83.3%) | 5 (83.3%) |
| Arthralgia | 1 (7.1%) | 0 | 0 | 1 (16.7%) | 6 (50.0%) | 1 (16.7%) | 0 |
| Upper respiratory tract infection | 3 (21.4%) | 1 (16.7%) | 1 (16.7%) | 0 | 2 (16.7%) | 0 | 3 (50.0%) |
| Nausea | 1 (7.1%) | 0 | 0 | 2 (33.3%) | 1 (8.3%) | 2 (33.3%) | 0 |
| Dizziness | 1 (7.1%) | 0 | 0 | 0 | 1 (8.3%) | 2 (33.3%) | 0 |
| Dysaesthesia | 0 | 0 | 0 | 0 | 3 (25.0%) | 0 | 0 |
| Fatigue | 0 | 0 | 0 | 0 | 2 (16.7%) | 0 | 1 (16.7%) |
| Flushing | 0 | 1 (16.7%) | 0 | 0 | 0 | 0 | 1 (16.7%) |
| Hyperaesthesia | 0 | 0 | 0 | 0 | 1 (8.3%) | 1 (16.7%) | 0 |
| Hypertension | 0 | 0 | 0 | 1 (16.7%) | 1 (8.3%) | 0 | 0 |
| Hypoaesthesia | 0 | 0 | 0 | 0 | 2 (16.7%) | 0 | 0 |
| Joint swelling | 0 | 0 | 0 | 0 | 2 (16.7%) | 0 | 0 |
| Pain in extremity | 0 | 0 | 0 | 0 | 0 | 0 | 2 (33.3%) |
| Pruritus | 0 | 1 (16.7%) | 0 | 0 | 1 (8.3%) | 0 | 0 |

[a] In decreasing frequency order based on frequency in REGN475 groups, combined
Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

### 3.1.4.2. Serious Adverse Events

One SAE was reported during this FIH study. A 58 year-old female subject (001-048) treated with REGN475 0.3 mg/kg SC experienced Acute Viral Bronchitis of moderate severity 102 days after receiving study drug. The event lasted for 3 days and resolved with treatment. The subject completed the study. The event was not considered by the investigator to be related to study treatment.

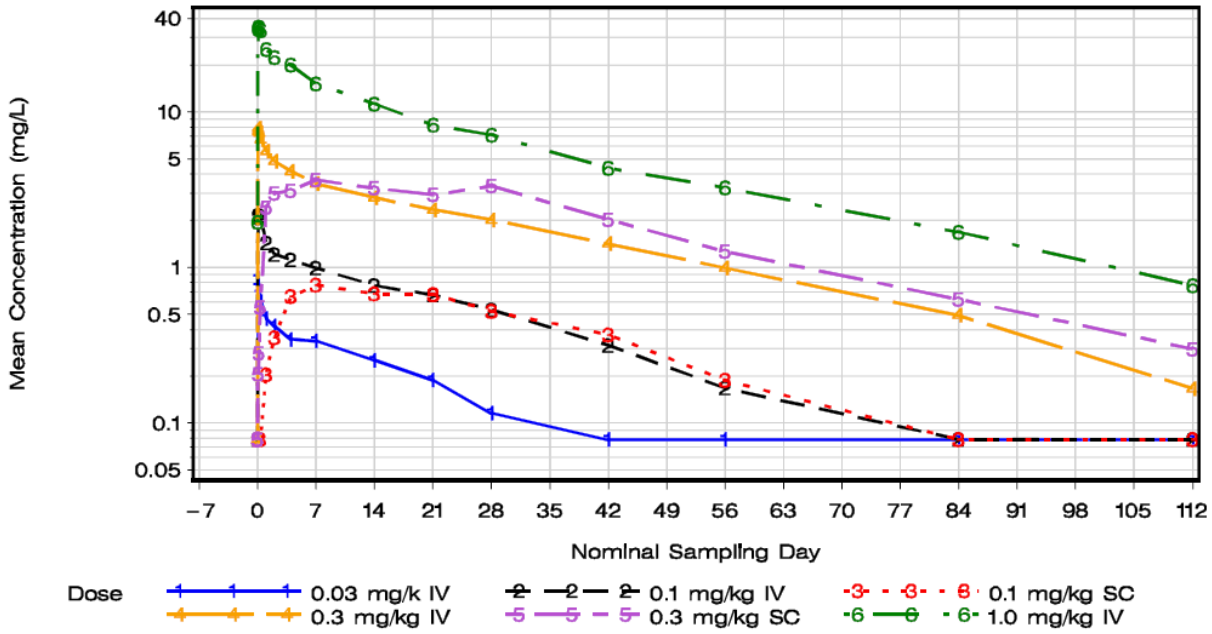
### 3.1.4.3. Joint Replacements

One patient treated in this study (1.0 mg/kg IV) required a knee replacement approximately 17 months after dosing. This patient had a history of bilateral knee OA for 3 years prior to study participation with 1 knee having a Kellgren-Lawrence grade of 3 at the time of the study, and the other knee having a Kellgren-Lawrence grade of 2. Additional information on this patient is presented in Section 4.

### 3.1.4.4. Clinical Pharmacokinetics

Mean concentrations of functional REGN475 observed in the R475-PN-0817 study are presented in Figure 7. Presumably, because the production rate of NGF is low, the target-mediated phase was not observed. The pharmacokinetics of REGN475 appears to be linear. Bioavailability was high (F = 82%).

**Figure 7: Log-scaled Mean Concentrations of Functional REGN475 vs. Nominal Time**




*Note: Concentrations below the lower limit of quantification (LLOQ) are imputed as LLOQ/2*

A listing of non-compartmental parameter estimates by route of administration is shown in Table 5.

Median CL, $t_{1/2}$, $V_z$, $V_{ss}$, $AUC_{last}$/dose, $AUC_{all}$/dose and $AUC_{inf}$/dose were similar across all REGN475 IV dose groups. This result is consistent with the hypothesis that the kinetics of REGN475 is linear.

Median $t_{1/2}$ was similar across the REGN475 SC dose groups. Median CL/F and Vz/F were approximately 2-fold higher in the REGN475 0.1 mg/kg SC group than in the 0.3 mg/kg SC group. The deviation from dose proportionality is likely due to between subject variability in volume of distribution.

**Table 5: Summary of Observed Non-compartmental Pharmacokinetic Parameters of Functional REGN475 by Route of Administration**

| Parameter | | N | Mean | SD | SE | CV% | Min | Median | Max |
|---|---|---|---|---|---|---|---|---|---|
| **IV** | **$t_{1/2}$ (day)** | 30 | 24.5 | 6.50 | 1.19 | 26.6 | 13.6 | 23.3 | 43.3 |
| | **CL (L/day/kg)** | 30 | 0.00207 | 0.000749 | 0.000137 | 36.1 | 0.000935 | 0.00193 | 0.00418 |
| | **$V_z$ (L/kg)** | 30 | 0.0688 | 0.0169 | 0.00308 | 24.5 | 0.0412 | 0.0697 | 0.111 |
| | **$V_{ss}$ (L/kg)** | 30 | 0.0648 | 0.0180 | 0.00328 | 27.7 | 0.0331 | 0.0653 | 0.110 |
| | **$C_{max}$/Dose (kg/L)** | 30 | 31.6 | 10.6 | 1.93 | 33.4 | 13.9 | 28.6 | 54.7 |
| | **$T_{max}$ (day)** | 30 | 0.119 | 0.116 | 0.0213 | 97.9 | 0.0424 | 0.0611 | 0.384 |
| | **$AUC_{last}$/Dose (day/L)** | 30 | 459 | 204 | 37.3 | 44.5 | 108 | 460 | 942 |
| | **$AUC_{all}$/Dose (day/L)** | 30 | 472 | 196 | 35.7 | 41.4 | 129 | 470 | 942 |
| | **$AUC_{inf}$/Dose (day/L)** | 30 | 540 | 184 | 33.6 | 34.1 | 239 | 519 | 1069 |
| | **$MRT_{inf}$ (day)** | 30 | 32.9 | 8.92 | 1.63 | 27.1 | 15.7 | 31.5 | 63.0 |
| **SC** | **$t_{1/2}$ (day)** | 12 | 25.4 | 4.54 | 1.31 | 17.9 | 15.3 | 25.3 | 30.8 |
| | **CL/F (L/day/kg)** | 12 | 0.00235 | 0.000865 | 0.000250 | 36.9 | 0.00118 | 0.00235 | 0.00349 |
| | **$V_z$/F (L/kg)** | 12 | 0.0838 | 0.0305 | 0.00880 | 36.4 | 0.0466 | 0.0779 | 0.140 |
| | **$C_{max}$/Dose (kg/L)** | 12 | 11.5 | 5.31 | 1.53 | 46.3 | 5.67 | 10.3 | 22.8 |
| | **$T_{max}$ (day)** | 12 | 11.8 | 8.92 | 2.58 | 75.8 | 2.09 | 7.04 | 28.1 |
| | **$AUC_{last}$/Dose (day/L)** | 12 | 422 | 202 | 58.2 | 47.8 | 209 | 368 | 770 |
| | **$AUC_{all}$/Dose (day/L)** | 12 | 443 | 195 | 56.2 | 44.0 | 236 | 394 | 770 |
| | **$AUC_{inf}$/Dose (day/L)** | 12 | 491 | 198 | 57.3 | 40.4 | 287 | 437 | 847 |
| | **$MRT_{inf}$ (day)** | 12 | 40.9 | 6.48 | 1.87 | 15.8 | 29.6 | 42.3 | 50.3 |

In summary, target-mediated clearance of REGN475 was not observed in this study. Consequently, kinetics of functional REGN475 is close to linear. Bioavailability was high (F = 82%).

- The $t_{1/2}$was similar across different dose groups and routes of administration. The mean $t_{1/2}$was equal to 24.5 and 25.4 days in the IV and SC groups, respectively.
- Exposure after IV administration of REGN475 was close to dose proportional, and a slight deviation from dose proportionality was observed after SC administration of REGN475.
- No persistent drop in concentrations of REGN475 was observed, which was consistent with the absence of anti-REGN475 antibodies.

## 3.2. Exploratory Study in Osteoarthritis of the Knee – R475-PN-0901

**Study Title:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Repeat-Dose Study of the Safety and Efficacy of REGN475 In Patients with Osteoarthritis of the Knee.

### 3.2.1. Study Design Overview

Study R475-PN-0901 was a double-blind, prospective study in which 217 patients with OA of the knee. and with walking knee pain ≥ 4 on a 0 to 10-point numeric rating scale (NRS) at the screening visit and subsequently at the baseline visit, were washed out after screening from all prior pain medications except acetaminophen, and at the baseline visit randomized to 1 of 4 treatment groups (1 placebo and 3 active). Randomization was stratified by baseline NRS walking knee pain scores (>7 and ≤ 7). Each patient received an IV dose of placebo or REGN475 at baseline (Day 1) and at Week 8 (Day 57) for a total of 2 doses. The REGN475 doses were 0.03, 0.1, and 0.3 mg/kg based upon the results of the FIH study.

Patients were observed for 16 weeks following the second dose of study drug to fully characterize the duration of analgesic effect (to Week 24; Day 169). Patients were asked to discontinue their pain medications prior to the baseline visit and for the duration of the 24-week study. Acetaminophen as rescue medication (up to 4 g/day on no more than 4 consecutive days) and low-dose aspirin for cardiac prophylaxis were allowed during the study.

### 3.2.2. Study Population

Eligible patients for this study were men and women between 40 and 75 years of age with a diagnosis of OA of the knee (The American College of Rheumatology criteria), and who had experienced moderate-to-severe knee pain for a period of ≥ 3 months (on average). Patients were required to have a Kellgren-Lawrence score of 2 or 3 in the index knee based on an x-ray taken within 6 months of enrollment and to weigh <110 kg.

### 3.2.3. Study Objectives

***Primary Objective***

The primary objective of the study was to assess the safety and tolerability of REGN475 compared with placebo after repeat administration in patients with OA of the knee.

The safety and tolerability of REGN475 were assessed from the incidence of TEAEs, clinical laboratory testing, vital signs, electrocardiograms (ECG's), physical examination findings, and neurological assessments of sensory (tactile, pain, and vibration) and motor (muscle strength and reflex) function. Treatment-emergent adverse events were defined as AEs starting after the first dose of study therapy and the completion of the study at the end of week 24 (Day 169).

***Secondary Objectives***

The secondary objectives of the study were:

- To explore the efficacy of REGN475 (knee pain, function, and QOL) in this patient population.

The effect of REGN475 on walking knee pain was assessed using an 11-point NRS. Patients were asked to report the average intensity of their walking knee pain daily for the duration of the

24-week study. Changes in OA status were assessed using the WOMAC, including pain, function, and stiffness subscales. The patient's assessment of overall treatment effect was assessed by the PGIC. The patients' QOL was evaluated using the SF-12 (Short Form 12-Item Questionnaire).

- To characterize the PK and immunogenicity profiles of REGN475 associated with repeat-dose administration.

### 3.2.4. Results: Osteoarthritis of the Knee

#### 3.2.4.1. Treatment-Emergent Adverse Events

The percentage of patients with at least 1 TEAE was similar in the placebo group (63.6%) and the 0.03 mg/kg group (66.1%), and was higher in the 0.1 and 0.3 mg/kg groups (75.0%) (Table 6). The percentage of patients with at least 1 study drug-related TEAE was lower in the placebo group (9.1%) than in the REGN475 groups (17.9% in the 0.03 mg/kg group, 26.9% in the 0.1 mg/kg group, and 25.0% in the 0.3 mg/kg group). Serious TEAEs were infrequent, occurring in 0 to 3 patients per treatment group. One patient who received placebo, 1 who received 0.03 mg/kg, and 5 who received 0.3 mg/kg discontinued the use of the study drug because of TEAEs. Two patients each in the placebo and 0.03 mg/kg groups, 1 patient in the 0.1 mg/kg group, and 6 patients in the 0.3 mg/kg group withdrew from the study because of TEAEs.

**Table 6: Summary of TEAEs (SAF) – R475-PN-0901: OA of the Knee**

| | Placebo (n=55) n (%) | REGN475 (0.03 mg/kg) (n=56) n (%) | REGN475 (0.1 mg/kg) (n=52) n (%) | REGN475 (0.3 mg/kg) (n=52) n (%) |
|---|---|---|---|---|
| Subjects with no TEAEs | 20 (36.4%) | 19 (33.9%) | 13 (25.0%) | 13 (25.0%) |
| | | | | |
| Subjects with at least one TEAE | 35 (63.6%) | 37 (66.1%) | 39 (75.0%) | 39 (75.0%) |
| | | | | |
| Subjects with study drug related TEAEs | 5 (9.1%) | 10 (17.9%) | 14 (26.9%) | 13 (25.0%) |
| | | | | |
| Subjects with serious TEAEs | 3 (5.5%) | 2 (3.6%) | 2 (3.8%) | 0 |
| | | | | |
| **Subjects with TEAEs resulting in discontinuation of study drug** | | | | |
| Subjects who discontinued study drug due to TEAEs | 1 (1.8%) | 1 (1.8%) | 0 | 5 (9.6%) |
| Subjects who discontinued study drug due to serious TEAE | 1 (1.8%) | 0 | 0 | 0 |
| | | | | |
| **Subjects with TEAEs resulting in discontinuation of study** | | | | |
| Subjects who discontinued study due to TEAEs | 2 (3.6%) | 2 (3.6%) | 1 (1.9%) | 6 (11.5%) |
| Subjects who discontinued study due to serious TEAEs | 1 (1.8%) | 1 (1.8%) | 0 | 0 |
| | | | | |
| Subjects who died | 0 | 0 | 0 | 0 |

Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

Arthralgia was the most frequent TEAE reported in REGN475 treated patients in this study (Table 7). The percentage of patients having Arthralgia was lower in the placebo and 0.03 mg/kg groups (5.5% and 3.6%, respectively) than in the 0.1 and 0.3 mg/kg groups (19.2% and 15.4%, respectively). Headache and Peripheral Edema were the second most frequently reported TEAEs in REGN475 treated patients. Headache was similarly frequent in all 4 treatment groups (7.1% to 7.7%). Peripheral Edema showed evidence of a dose relationship, with frequency ranging from 1.8% in the placebo group to 9.6% in the 0.3 mg/kg group, although the numbers of patients affected were small. Joint Swelling occurred in 6.9% of patients treated with REGN475 and in none of the patients in the placebo group. Myalgia was more frequent in the 0.3 mg/kg group (9.6%) than in the other 3 groups (1.8% to 3.8%). In all 4 treatment groups studied, most of the TEAEs were mild or moderate.

The percentage of patients with neurosensory or neuromuscular events was similar for the placebo and 0.03 mg/kg groups, higher for the 0.1 mg/kg group, and highest for the 0.3 mg/kg group (Table 7). As noted previously, Arthralgia was less frequent in the placebo and 0.03 mg/kg groups than in the 0.1 and 0.3 mg/kg groups, and Myalgia was more frequent in the 0.3 mg/kg

group than in the other 3 groups. Hyperesthesia and Pallanaesthesia were more frequent in the 0.3 mg/kg group than in the other groups. Hypoesthesia, Hyperreflexia, and Hyporeflexia were reported in REGN475-treated patients and not in patients in the placebo group. None of the TEAEs of interest were serious, although Arthralgia and Hyperesthesia led to withdrawal in some cases (see Section 3.2.4.3). None of these TEAEs were considered severe in intensity.

Across REGN475 groups, the percentage of patients with severe TEAEs ranged from zero in the 0.3 mg/kg group to 5.8% (3 patients) in the 0.1 mg/kg group. The severe TEAEs were Pyelonephritis, Retinal Detachment, Retinal Tear, and Atrial Fibrillation in the placebo group, and Headache, Myalgia, OA, Joint Effusion, Pulmonary Embolism, and Deep Vein Thrombosis in the REGN475 groups.

**Table 7: Summary of TEAEs Reported by at Least 2% of Patients Treated with REGN475 (SAF) – R475-PN-0901: OA of the Knee**

| MedDRA Preferred Term [a] | Placebo (n=55) n (%) | REGN475 (0.03mg/kg) (n=56) n (%) | REGN475 (0.1 mg/kg) (n=52) n (%) | REGN475 (0.3 mg/kg) (n=52) n (%) |
|---|---|---|---|---|
| Subjects with at least one adverse event | 35 (63.6%) | 37 (66.1%) | 39 (75.0%) | 39 (75.0%) |
| Arthralgia | 3 (5.5%) | 2 (3.6%) | 10 (19.2%) | 8 (15.4%) |
| Headache | 4 (7.3%) | 4 (7.1%) | 4 (7.7%) | 4 (7.7%) |
| Edema peripheral | 1 (1.8%) | 3 (5.4%) | 4 (7.7%) | 5 (9.6%) |
| Joint swelling | 0 | 2 (3.6%) | 5 (9.6%) | 4 (7.7%) |
| Nasopharyngitis | 1 (1.8%) | 5 (8.9%) | 4 (7.7%) | 1 (1.9%) |
| Hypoaesthesia | 0 | 3 (5.4%) | 2 (3.8%) | 4 (7.7%) |
| Upper respiratory tract infection | 4 (7.3%) | 3 (5.4%) | 2 (3.8%) | 4 (7.7%) |
| Myalgia | 2 (3.6%) | 1 (1.8%) | 2 (3.8%) | 5 (9.6%) |
| Back pain | 3 (5.5%) | 1 (1.8%) | 2 (3.8%) | 4 (7.7%) |
| Bronchitis | 0 | 3 (5.4%) | 3 (5.8%) | 1 (1.9%) |
| Pain in extremity | 1 (1.8%) | 2 (3.6%) | 1 (1.9%) | 4 (7.7%) |
| Pallanaesthesia | 2 (3.6%) | 2 (3.6%) | 1 (1.9%) | 4 (7.7%) |
| Areflexia | 1 (1.8%) | 2 (3.6%) | 1 (1.9%) | 3 (5.8%) |
| Diarrhea | 2 (3.6%) | 3 (5.4%) | 2 (3.8%) | 1 (1.9%) |
| Hyporeflexia | 0 | 4 (7.1%) | 1 (1.9%) | 1 (1.9%) |
| Pain | 1 (1.8%) | 1 (1.8%) | 2 (3.8%) | 3 (5.8%) |
| Paraesthesia | 3 (5.5%) | 3 (5.4%) | 0 | 3 (5.8%) |
| Hyperaesthesia | 1 (1.8%) | 0 | 0 | 5 (9.6%) |
| Hyperreflexia | 0 | 0 | 3 (5.8%) | 2 (3.8%) |
| Sinusitis | 3 (5.5%) | 1 (1.8%) | 3 (5.8%) | 1 (1.9%) |
| Blood pressure increased | 0 | 3 (5.4%) | 1 (1.9%) | 0 |
| Cough | 1 (1.8%) | 0 | 3 (5.8%) | 1 (1.9%) |
| Dizziness | 0 | 2 (3.6%) | 0 | 2 (3.8%) |
| Influenza | 1 (1.8%) | 1 (1.8%) | 3 (5.8%) | 0 |

[a] In decreasing frequency order based on frequency in REGN475 groups, combined
Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

### 3.2.4.2. Serious Adverse Events

Serious TEAEs occurred in 3 of 55 (5.5%) patients in the placebo group and 4 of 160 (2.5%) patients in the combined REGN475 groups (Table 8). The serious TEAEs reported in the placebo group were Pyelonephritis, Retinal Detachment, Retinal Tear, and Atrial Fibrillation; those reported in the REGN475 groups were Headache, Myalgia, Osteoarthritis, Joint Effusion, Pulmonary Embolism, and Deep Vein Thrombosis.

**Table 8: Summary of Treatment-Emergent Serious Adverse Events (SAF) – R475-PN-0901: OA of the Knee**

| System Organ Class<br>MedDRA Preferred Term | Placebo (n=55) n (%) | REGN475 (0.03 mg/kg) (n=56) n (%) | REGN475 (0.1 mg/kg) (n=52) n (%) | REGN475 (0.3 mg/kg) (n=52) n (%) |
|---|---|---|---|---|
| Subjects with at least one serious adverse event | 3 (5.5%) | 2 (3.6%) | 2 (3.8%) | 0 |
| | | | | |
| Musculoskeletal and connective tissue disorders | 1 (1.8%) | 1 (1.8%) | 1 (1.9%) | 0 |
| Osteoarthritis | 0 | 1 (1.8%) | 1 (1.9%) | 0 |
| Intervertebral disc degeneration | 1 (1.8%) | 0 | 0 | 0 |
| | | | | |
| Neoplasms benign, malignant and unspecified | 0 | 1 (1.8%) | 0 | 0 |
| Squamous cell carcinoma | 0 | 1 (1.8%) | 0 | 0 |
| | | | | |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 1 (1.9%) | 0 |
| Pulmonary embolism | 0 | 0 | 1 (1.9%) | 0 |
| | | | | |
| Vascular disorders | 0 | 0 | 1 (1.9%) | 0 |
| Deep vein thrombosis | 0 | 0 | 1 (1.9%) | 0 |
| | | | | |
| Cardiac disorders | 1 (1.8%) | 0 | 0 | 0 |
| Atrial fibrillation | 1 (1.8%) | 0 | 0 | 0 |
| | | | | |
| Infections and infestations | 1 (1.8%) | 0 | 0 | 0 |
| Pyelonephritis | 1 (1.8%) | 0 | 0 | 0 |

### 3.2.4.3. Adverse Events Leading to Withdrawal

Seven TEAEs resulted in discontinuation of study drug (that is, receipt of 1 dose rather than the planned 2 doses) by 7 patients: 1 in the placebo group, 1 in the 0.03 mg/kg group, and 5 in the 0.3 mg/kg group.) Contributing to the higher number of patients discontinuing study drug in the 0.3 mg/kg group were Hyperesthesia in 2 patients and Arthralgia and Pain in Extremity, each in 1 patient. One of the TEAEs resulting in discontinuation of study drug, Atrial Fibrillation, was serious. The TEAEs that resulted in discontinuation of study drug also resulted in withdrawal from the study, with 1 exception. A patient in the 0.3 mg/kg group had a Road Traffic Accident, did not receive a second dose of study drug, and was lost to follow-up.) The TEAEs that resulted in withdrawal from the study consisted of those that led to discontinuation of study drug (except for Road Traffic Accident), 3 additional cases of Arthralgia (1 each in the placebo, 0.1 mg/kg, and 0.3 mg/kg groups), and 1 case each of OA (0.03 mg/kg group), and Foot Fracture (0.3 mg/kg group). Eleven TEAEs resulted in withdrawal from the study by 11 patients: 6 patients (11.5%) in the 0.3 mg/kg group and 1 to 2 patients (1.9% to 3.6%) in the other 3 groups (Table 9).

**Table 9: Summary of TEAEs Resulting in Withdrawal from the Study (SAF) – R475-PN-0901: OA of the Knee**

| System Organ Class<br>MedDRA Preferred Term | Placebo (N=55)<br>n (%) | REGN475 (0.03 mg/kg) (N=56)<br>n (%) | REGN475 (0.1 mg/kg) (N=52)<br>n (%) | REGN475 (0.3 mg/kg) (N=52)<br>n (%) | All REGN475 Doses Combined (N=160)<br>n (%) |
|---|---|---|---|---|---|
| Subjects with at least one adverse event resulting in discontinuation | 2 (3.6%) | 2 (3.6%) | 1 (1.9%) | 6 (11.5%) | 9 (5.6%) |
| Musculoskeletal and connective tissue disorders | 1 (1.8%) | 1 (1.8%) | 1 (1.9%) | 3 (5.8%) | 5 (3.1%) |
| Arthralgia | 1 (1.8%) | 0 | 1 (1.9%) | 2 (3.8%) | 3 (1.9%) |
| Osteoarthritis | 0 | 1 (1.8%) | 0 | 0 | 1 (0.6%) |
| Pain in extremity | 0 | 0 | 0 | 1 (1.9%) | 1 (0.6%) |
| Injury, poisoning and procedural complications | 0 | 1 (1.8%) | 0 | 1 (1.9%) | 2 (1.3%) |
| Foot fracture | 0 | 0 | 0 | 1 (1.9%) | 1 (0.6%) |
| Tendon rupture | 0 | 1 (1.8%) | 0 | 0 | 1 (0.6%) |
| Nervous system disorders | 0 | 0 | 0 | 2 (3.8%) | 2 (1.3%) |
| Hyperaesthesia | 0 | 0 | 0 | 2 (3.8%) | 2 (1.3%) |
| Cardiac disorders | 1 (1.8%) | 0 | 0 | 0 | 0 |
| Atrial fibrillation | 1 (1.8%) | 0 | 0 | 0 | 0 |

Note: MedDRA (Version 12.0) coding dictionary applied.
Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and last dose plus 112 days.
The table is sorted by descending order of frequency of system organ class and preferred term for All REGN475 Subjects Combined.

#### 3.2.4.4. Joint Replacements

Eleven patients treated in this study required TJRs. Two of these joint replacements took place during the study. The remainder of the joint replacements took place between 7 and 17 months following dosing. Of the 11 patients, 10 had received active treatment (representing 6.3% of the 160 patients treated with REGN475) and 1 had received placebo (1.8% of 55 placebo patients). Seven of the TJR's occurred in the index joint being studied (knee). Of the remaining 4 joints, 3 were non-index knees and 1 was a hip. There were no unique characteristics to identify patients who ultimately underwent TJR. Additional information about these cases can be found in Section 4.

#### 3.2.4.5. Summary of Efficacy

Efficacy of REGN475 in OA of the knee was explored via daily assessments of walking knee pain intensity. Assessment of changes in WOMAC (pain, stiffness, and function), patient's PGIC and QoL were conducted at specified clinic visits. Because the 2 administrations of study drug were 8 weeks apart, a time integrated approach to the data was deemed to be of greater interest than the analyses at discrete time points. The results of both these approaches were similar and therefore, consistent with the results being provided by the other sponsors, the analyses at discrete time points are provided in this document. For the primary endpoint and for the WOMAC and PGIC, the prespecified analytic method was the mixed-effect model of repeated measures (MMRM); sensitivity analyses included analysis of covariance (ANCOVA) using last observation carried forward (LOCF) to impute missing values and ANCOVA using baseline observation carried forward (BOCF) to impute missing values. For the QOL assessment (SF-12), the ANCOVA/LOCF approach was used.

All 3 dose levels of REGN475 (0.03, 0.1 and 0.3 mg/kg IV), were associated with greater improvement compared with placebo in change from baseline in walking knee pain (the key efficacy endpoint). The differences from placebo were statistically significant from baseline to week 8 and baseline to week 16 for the 0.1 mg/kg group, and from baseline to week 8 or week 16 for the 0.3 and 0.03 mg/kg groups, respectively (Figure 8 and Table 10). In the time-integrated approach, differences from placebo were statistically significant from baseline to week 8 and baseline to week 16 for the 0.1 and 0.3 mg/kg groups, and from baseline to week 16 for the 0.03 mg/kg group. Results for the per protocol set using observed data and for the full analysis set (FAS) using LOCF were similar to results for the FAS using observed data and analyzed by MMRM. In a subgroup analysis, results were similar for patients with baseline NRS $\leq$7 and those with baseline NRS >7. Consistent with the limited power of this exploratory study, results using the BOCF method were less robust.

Results for standardized total WOMAC score, pain subscale, and function subscale (observed data and LOCF) and for WOMAC stiffness subscale (observed data) were supportive of the results for walking knee pain NRS, indicating improvement after treatment with REGN475 compared with placebo. Improvements in WOMAC scores tended to be greater and more prolonged in the 0.1 and 0.3 mg/kg groups than in the 0.03 mg/kg group (Figure 9, Table 11, Table 12, and Table 13).

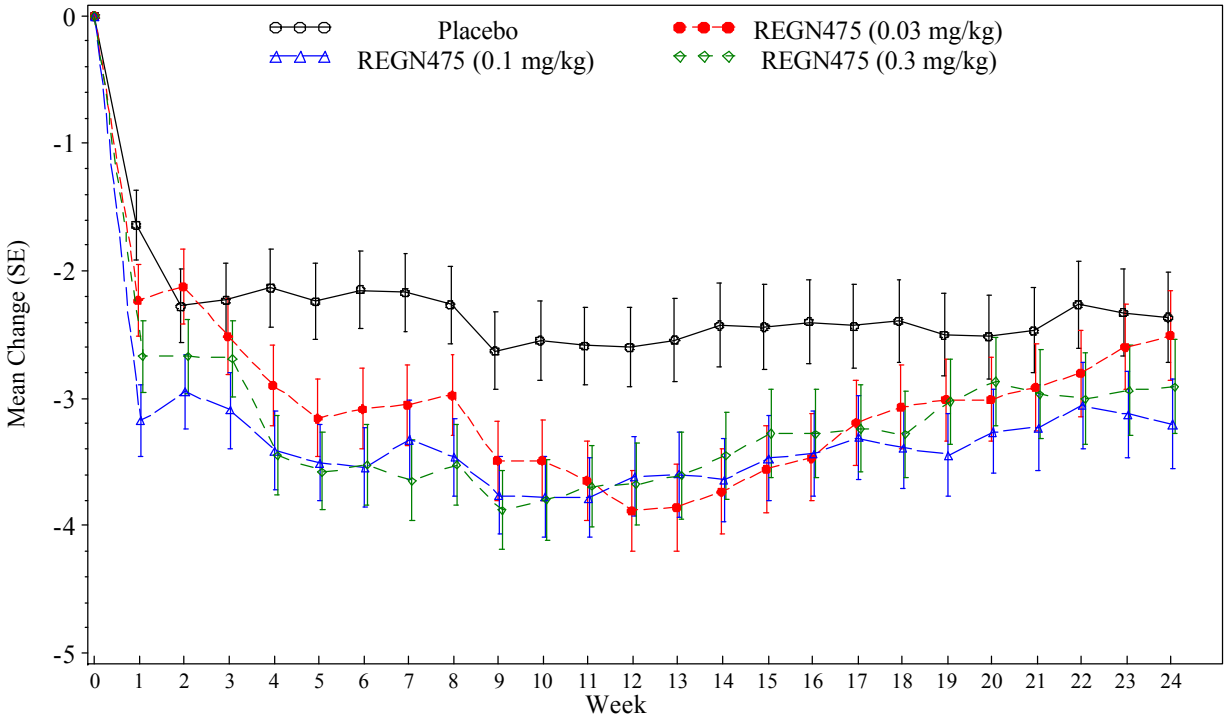
In landmark analysis, nominal p-values for the differences from placebo were <0.05 at weeks 8 for all 3 REGN475 groups and at week 16 for the 0.03 and 0.3 mg/kg groups (Table 14). In

time-integrated results for PGIC (observed data and LOCF), the nominal p-values for the differences from placebo were <0.05 at weeks 8 and 16 for all 3 REGN475 groups. The LS mean differences from placebo were greater in the 0.03 mg/kg group than in the other 2 REGN475 groups at week 16, were less in the 0.03 mg/kg group than in the other 2 groups at weeks 1 and 12, and were similar across the 3 REGN475 groups at other time points.

Use of rescue medication (acetaminophen) was more prevalent in the placebo group than in the 0.03 and 0.1 mg/kg groups after the first several weeks of the study and was less prevalent in the 0.3 mg/kg group than in the other 3 groups throughout the study.

In summary (Table 15), exploratory efficacy results from this study show a durable, statistically and clinically meaningful effect of REGN475 in reducing walking knee pain and improving function in this small study population of patients with OA.

**Figure 8: Mean Change in Weekly NRS from Baseline to Week 16 – LS Means (FAS) – R475-PN-0901: OA of the Knee**



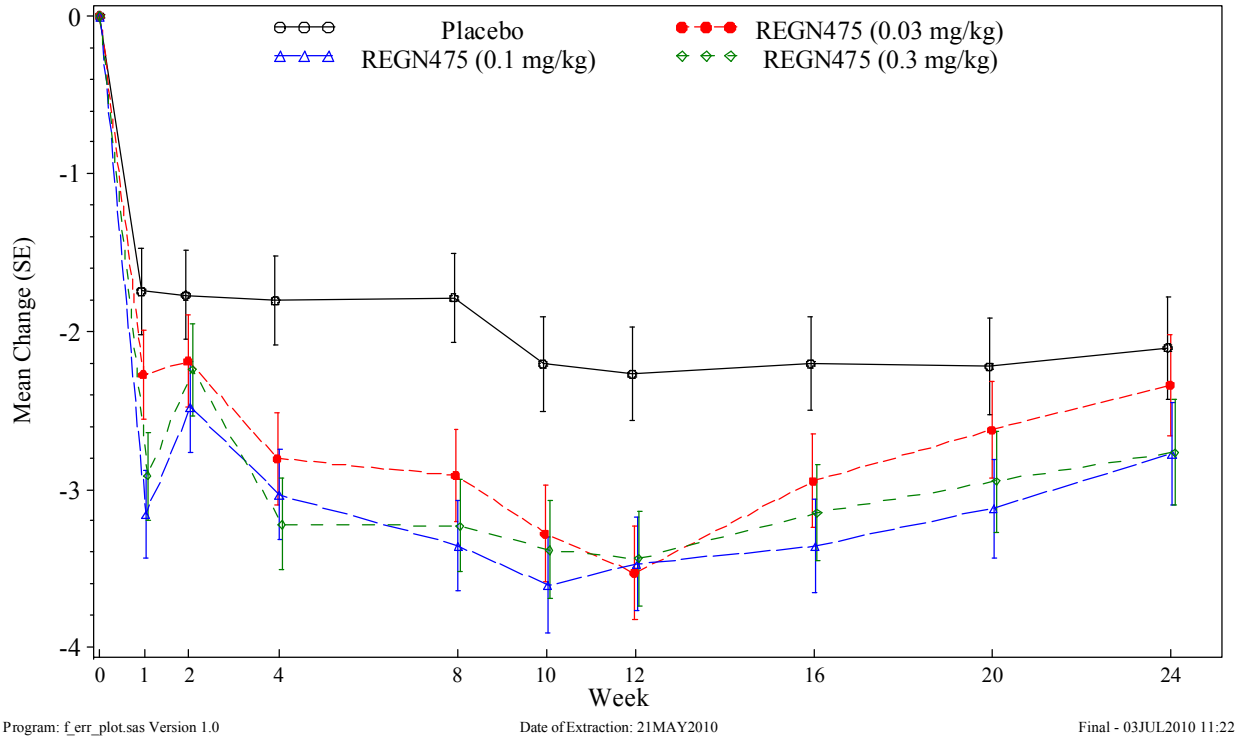

***Patients were dosed at Baseline and Week 8.***

**Table 10: Change from Baseline to Week 16 in Walking Knee Pain NRS Scores; Observed Data Using MMRM (FAS) – R475-PN-0901: OA of the Knee**

| | **Treatment Groups** | | | |
|---|---|---|---|---|
| | **Placebo (n = 55 )** | **REGN475 0.03 mg/kg (n = 53)** | **REGN475 0.1 mg/kg (n = 53)** | **REGN475 0.3 mg/kg (n = 54 )** |
| Baseline Walking Knee Pain (SD) | 6.4 (1.69) | 6.6 (1.65) | 6.5 (1.53) | 6.6 (1.47) |
| *Week 8* | | | | |
| Mean Change from Baseline to Week 8 (SD) | -2.1 (2.08) | -2.8 (2.29) | -3.3 (2.61) | -3.6 (2.48) |
| Diff vs. Placebo LS Means (SE) | | -0.7 (0.43) | -1.2 (0.42) | -1.3 (0.43) |
| P value | | 0.0981 | 0.0053 | 0.0035 |
| *Week 16* | | | | |
| Mean Change from Baseline to Week 16 (SD) | -2.5 (2.15) | -3.4 (2.24) | -3.4 (2.58) | -3.3 (2.55) |
| Diff vs. Placebo LS Means (SE) | | -1.1 (0.46) | -1.0 (0.46) | -0.9 (0.47) |
| P value | | 0.0229 | 0.0267 | 0.0631 |

Data captured using NRS. P-values via MMRM (Mixed-Effects Model – Repeated Measures)

**Figure 9: Mean Change in Standardized Total WOMAC Score from Baseline – Observed Data (FAS) – R475-PN-0901: OA of the Knee**




Patients were dosed at Baseline and Week 8.

**Table 11: WOMAC Pain Subscale - Change from Baseline to Week 16; Observed Data Using MMRM (FAS) – R475-PN-0901: OA of the Knee**

| | **Treatment Groups** | | | |
|---|---|---|---|---|
| | **Placebo (n = 55 )** | **REGN475 0.03 mg/kg (n = 53)** | **REGN475 0.1 mg/kg (n = 53)** | **REGN475 0.3 mg/kg (n = 54 )** |
| Baseline Pain Score (SD) | 5.9 (1.79) | 5.7 (1.77) | 6.1 (1.75) | 6.4 (1.97) |
| *Week 8* | | | | |
| Mean Change from Baseline to Week 8 (SD) | -1.9 (1.74) | -2.6 (2.01) | -3.4 (2.54) | -3.5 (2.42) |
| Diff vs. Placebo LS Means (SE) | | -0.9 (0.39) | -1.4 (0.39) | -1.3 (0.39) |
| P value | | 0.0228 | 0.0003 | 0.0010 |
| *Week 16* | | | | |
| Mean Change from Baseline to Week 16 (SD) | -2.4 (2.18) | -2.7 (1.89) | -3.4 (2.53) | -3.2 (2.24) |
| Diff vs. Placebo LS Means (SE) | | -0.6 (0.42) | -1.1 (0.42) | -0.8 (0.42) |
| P value | | 0.1486 | 0.0090 | 0.0488 |

Data captured using NRS. P-values via MMRM (Mixed-Effects Model – Repeated Measures)

**Table 12: WOMAC Function Subscale - Change from Baseline to Week 16; Observed Data Using MMRM (FAS) – R475-PN-0901: OA of the Knee**

| | Treatment Groups | | | |
|---|---|---|---|---|
| | **Placebo (n = 55 )** | **REGN475 0.03 mg/kg (n = 53)** | **REGN475 0.1 mg/kg (n = 53)** | **REGN475 0.3 mg/kg (n = 54 )** |
| Baseline Function Score (SD) | 5.9 (1.75) | 5.9 (1.83) | 6.2 (1.67) | 6.2 (2.07) |
| *Week 8* | | | | |
| Mean Change from Baseline to Week 8 (SD) | -1.8 (1.95) | -2.8 (2.07) | -3.4 (2.32) | -3.4 (2.57) |
| Diff vs. Placebo LS Means (SE) | | -1.2 (0.41) | -1.6 (0.40) | -1.4 (0.40) |
| P value | | 0.0037 | 0.0001 | 0.0005 |
| *Week 16* | | | | |
| Mean Change from Baseline to Week 16 (SD) | -2.3 (2.30) | -2.9 (1.78) | -3.4 (2.28) | -3.1 (2.18) |
| Diff vs. Placebo LS Means (SE) | | -0.8 (0.41) | -1.1 (0.41) | -0.9 (0.42) |
| P value | | 0.0693 | 0.0071 | 0.0245 |

Data captured using NRS. P-values via MMRM (Mixed-Effects Model – Repeated Measures) )

**Table 13: WOMAC Stiffness Subscale - Change from Baseline to Week 16; Observed Data Using MMRM (FAS) – R475-PN-0901: OA of the Knee**

| | **Treatment Groups** | | | |
|---|---|---|---|---|
| | **Placebo (n = 55 )** | **REGN475 0.03 mg/kg (n = 53)** | **REGN475 0.1 mg/kg (n = 53)** | **REGN475 0.3 mg/kg (n = 54 )** |
| Baseline Mean Stiffness Score (SD) | 6.3 (1.92) | 6.4 (2.03) | 6.4 (1.88) | 6.8 (1.96) |
| *Week 8* | | | | |
| Mean Change from Baseline to Week 8 (SD) | -2.0 (2.11) | -2.9 (2.43) | -3.8 (2.81) | -3.9 (2.88) |
| Diff vs. Placebo LS Means (SE) | | -1.1 (0.44) | -1.8 (0.44) | -1.7 (0.44) |
| P value | | 0.0118 | <0.0001 | 0.0002 |
| *Week 16* | | | | |
| Mean Change from Baseline to Week 16 (SD) | -2.4 (2.43) | -3.1 (1.96) | -3.6 (2.67) | -3.5 (2.54) |
| Diff vs. Placebo LS Means (SE) | | -0.9 (0.45) | -1.4 (0.45) | -1.1 (0.46) |
| P value | | 0.0380 | 0.0031 | 0.0212 |

Data captured using NRS. P-values via MMRM (Mixed-Effects Model – Repeated Measures)

**Table 14: Patients Global Impression of Change at Week 8 and 16--- Observed Data Using MMRM (FAS) – R475-PN-0901: OA of the Knee**

| Week | Placebo (n=55) | REGN475 (0.03 mg/kg) (n=53) | REGN475 (0.1 mg/kg) (n=53) | REGN475 (0.3 mg/kg) (n=54) |
|---|---|---|---|---|
| **Week 8** | | | | |
| n | 51 | 50 | 50 | 46 |
| Mean Score (SD) | 3.1 (1.21) | 2.3 (1.00) | 2.1 (1.10) | 2.1 (0.98) |
| Min : Max | 1 : 6 | 1 : 4 | 1 : 5 | 1 : 4 |
| Difference vs. placebo [1] | | | | |
| LS Means (SE) | | -0.8 (0.21) | -1.0 (0.21) | -0.9 (0.21) |
| 95% CI | | -1.2 : -0.4 | -1.4 : -0.6 | -1.4 : -0.5 |
| P-value | | 0.0002 | <0.0001 | <0.0001 |
| **Week 16** | | | | |
| n | 44 | 47 | 43 | 41 |
| Mean Score (SD) | 2.8 (1.32) | 2.2 (0.95) | 2.5 (1.26) | 2.4 (1.16) |
| Min : Max | 1 : 7 | 1 : 5 | 1 : 6 | 1 : 5 |
| Difference vs. placebo [1] | | | | |
| LS Means (SE) | | -0.7 (0.24) | -0.4 (0.24) | -0.5 (0.25) |
| 95% CI | | -1.1 : -0.2 | -0.9 : 0.1 | -1.0 : -0.1 |
| P-value | | 0.0056 | 0.1168 | 0.0297 |

**Table 15: Summary of Efficacy Endpoints: Change from Baseline to Week 16† - R475-PN-0901 OA of the Knee**

| Endpoint | Placebo (n=55) n (%) | REGN475 (0.03 mg/kg) (n=53) n (%) | REGN475 (0.1 mg/kg) (n=53) n (%) | REGN475 (0.3 mg/kg) (n=54) n (%) |
|---|---|---|---|---|
| Walking Knee Pain | -2.5 | -3.4* | -3.4* | -3.3 |
| WOMAC (total) | -2.3 | -2.9 | -3.4** | -3.2* |
| WOMAC pain | -2.4 | -2.7 | -3.4** | -3.2* |
| WOMAC function | -2.3 | -2.9 | -3.4** | -3.1* |
| WOMAC stiffness | -2.4 | -3.1* | -3.6** | -3.5* |
| PGIC (at Week 16) | 2.8 | 2.2** | 2.5 | 2.4* |
| QOL (SF-12) (physical/mental) | 6.1/3.5 | 9.7/-0.4*^ | 8.4/2.5 | 9.2*/0.2 |

* $p<0.05$
** $p<0.01$
^ Significantly inferior to placebo
† Change from Baseline to week 16 except for PGIC at week 16

## 3.3. Exploratory Study in Sciatic Pain – R475-PN-0908

**Study Title:** A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Safety and Efficacy of Subcutaneously Administered REGN475 in Patients with Sciatic Pain

### 3.3.1. Study Design Overview

Study R475-PN-0908 was a double-blind, prospective study in which patients with sciatic pain were randomized to 1 of 3 treatment groups (1 placebo and 2 active). Each patient received a single SC dose of placebo or REGN475 at baseline (Day 1). The REGN475 doses were 0.1 and 0.3 mg/kg. Patients were followed for 12 weeks after their dose of study drug. Patients were allowed to maintain their current 'standard of care' treatment regimen for the duration of the study.

### 3.3.2. Study Population

Eligible patients for this study were adult men and women up to age 65 experiencing unilateral, moderate-to-severe sciatic pain (≥ 4 on the NRS), for a period of at least 2 weeks but no more than 16 weeks. The pattern of pain needed to be consistent with L4, L5 or S1 radiculopathy and the straight leg raising test had to be positive.

### 3.3.3. Study Objectives

***Primary Objective***

The primary objective of the study was to compare the analgesic efficacy of REGN475 to placebo as an adjunct to standard of care therapy in patients with sciatic pain. The primary endpoint was reduction in the area under the curve for average daily pain score from baseline to week 4.

***Secondary Objectives***

- To assess the safety and tolerability of REGN475
- To assess the impact of REGN475 on daily functioning using the Oswestry Disability Questionnaire
- To assess the impact of REGN475 on concomitant analgesic use.
- To assess the PK profile of a single SC dose of REGN475.

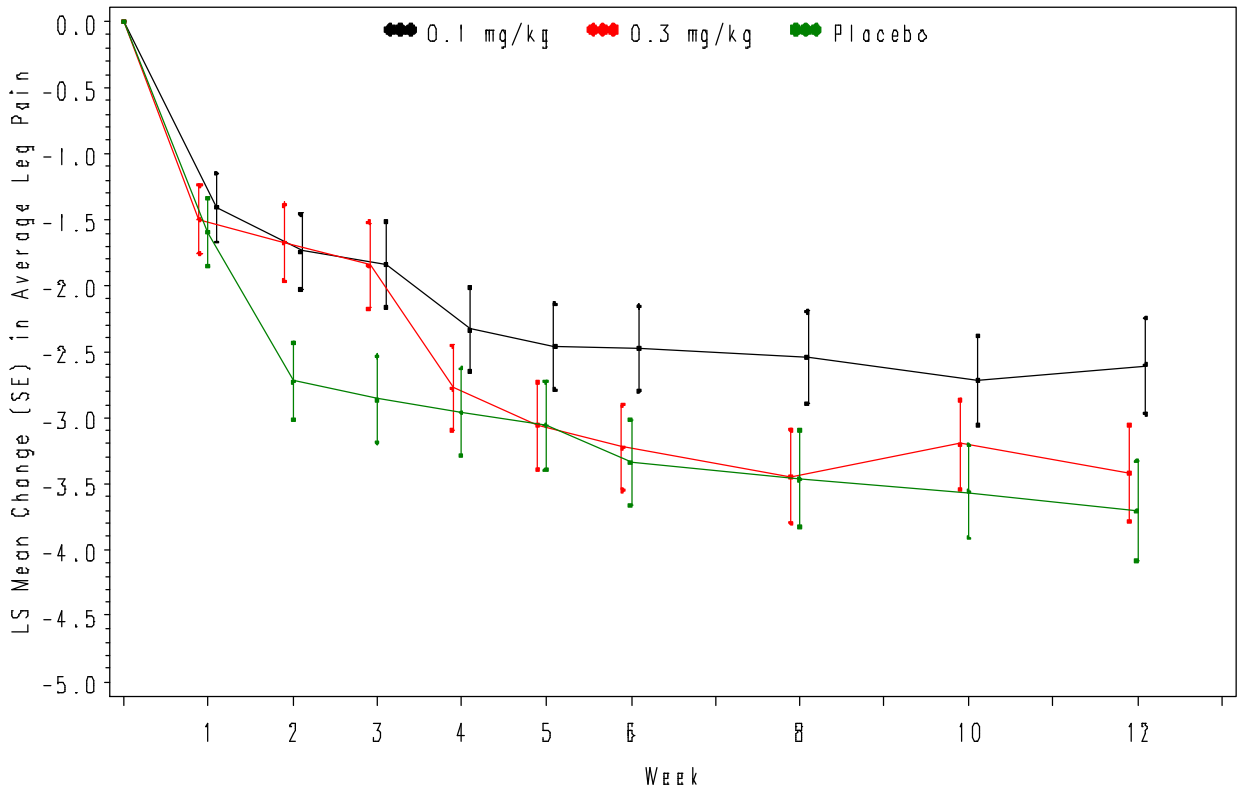
### 3.3.4. Results: Sciatic Pain

#### 3.3.4.1. Summary of Efficacy

Patients in the R475-PN-0908 study of sciatic pain rated their leg and back pain using a NRS at the screening and baseline visits, daily for 6 weeks following drug administration at baseline, and at each study visit thereafter. Daily NRS assessments (made during the 6 weeks following baseline) were collected using an interactive voice response system (IVRS). Patients completed the Oswestry Disability Questionnaire at baseline and each post-baseline clinic visit; and the PGIC was completed at each post-baseline visit.

The results of the primary and secondary efficacy analyses in this study are provided in Figure 10, Table 16, Table 17, and Table 18. The data showed that the 2 REGN475 doses evaluated in patients with sciatic pain (0.1 mg/kg and 0.3 mg/kg) did not demonstrate statistically significant treatment effects as compared with placebo on any efficacy endpoint.

**Figure 10: LS Mean Change in Weekly NRS of "Average" Leg Pain (FAS) – R475-PN-0908: Sciatic Pain**




Single-dose study. Patients were dosed at Baseline.

**Table 16: Area Under the Curve of Average Leg Pain, as Measured by the Daily Numeric Rating Scale, from Baseline to Week 4 (FAS) – R475-PN-0908: Sciatic Pain**

| | Placebo (n=51) n (%) | REGN475 0.1 mg/kg (n=53) n (%) | REGN475 0.3 mg/kg (n=53) n (%) |
|---|---|---|---|
| **Baseline Average leg pain NRS score** | | | |
| n | 51 | 53 | 53 |
| Mean Score (SD) | 6.2 (1.45) | 6.0 (1.24) | 6.1 (1.37) |
| Min : Max | 4 : 9 | 4 : 9 | 4 : 9 |
| **NRS-AUC at Week 4** | | | |
| n | 51 | 53 | 53 |
| Mean Score (SD) | 96.8 (55.99) | 112.7 (58.29) | 112.4 (55.81) |
| Min : Max | 4 : 219 | 6 : 232 | 7 : 217 |
| **LS Mean Difference vs. Placebo**[a] | | | |
| Difference (SE) | | 19.9 (10.54) | 17.8 (10.52) |
| 95% CI | | -0.9;40.7 | -3.0;38.6 |
| P-value | | 0.0610 | 0.0923 |

[a] ANCOVA model included treatment and stratum of duration of pain as fixed factors, baseline NRS as covariate.

**Table 17: Change in Oswestry Disability Questionnaire Score from Baseline – Observed Data Using MMRM (FAS) – R475-PN-0908: Sciatic Pain**

| | **Placebo (N = 51)** | **REGN475 (0.1 mg/kg) (N = 53)** | **REGN475 (0.3 mg/kg) (N = 53)** |
|---|---|---|---|
| Baseline | | | |
| n | 51 | 53 | 53 |
| Mean (SD) | 0.4 (0.14) | 0.4 (0.14) | 0.4 (0.16) |
| Week 1 change from baseline | | | |
| n | 49 | 52 | 53 |
| Mean (SD) | -0.1 (0.14) | -0.1 (0.13) | -0.1 (0.10) |
| Week 2 change from baseline | | | |
| n | 48 | 50 | 51 |
| Mean (SD) | -0.1 (0.13) | -0.1 (0.15) | -0.1 (0.12) |
| Week 3 change from baseline | | | |
| n | 46 | 51 | 51 |
| Mean (SD) | -0.1 (0.16) | -0.1 (0.14) | -0.1 (0.14) |
| Week 4 change from baseline | | | |
| n | 45 | 52 | 50 |
| Mean (SD) | -0.1 (0.17) | -0.1 (0.14) | -0.2 (0.13) |
| Week 6 change from baseline | | | |
| n | 45 | 50 | 48 |
| Mean (SD) | -0.2 (0.16) | -0.1 (0.15) | -0.2 (0.12) |
| Week 8 change from baseline | | | |
| n | 45 | 51 | 48 |
| Mean (SD) | -0.2 (0.16) | -0.2 (0.15) | -0.2 (0.13) |
| Week 10 change from baseline | | | |
| n | 45 | 49 | 47 |
| Mean (SD) | -0.2 (0.17) | -0.2 (0.15) | -0.2 (0.14) |
| Week 12 change from baseline | | | |
| n | 44 | 50 | 47 |
| Mean (SD) | -0.2 (0.19) | -0.2 (0.17) | -0.2 (0.14) |

**Table 18: Patient Global Impression of Change – Observed Data Using MMRM (FAS) – R475-PN-0908: Sciatic Pain**

| | Placebo (N = 51) | REGN475 (0.1 mg/kg) (N = 53) | REGN475 (0.3 mg/kg) (N = 53) |
|---|---|---|---|
| Week 1 | | | |
| n | 49 | 52 | 53 |
| Mean (SD) | 2.9 (1.12) | 2.9 (1.12) | 2.8 (1.22) |
| Week 2 | | | |
| n | 48 | 50 | 51 |
| Mean (SD) | 3.0 (1.18) | 2.8 (1.20) | 3.1 (1.39) |
| Week 3 | | | |
| n | 46 | 50 | 51 |
| Mean (SD) | 3.0 (1.22) | 2.7 (1.16) | 3.1 (1.38) |
| Week 4 | | | |
| n | 45 | 52 | 50 |
| Mean (SD) | 3.0 (1.10) | 2.8 (1.18) | 2.6 (1.03) |
| Week 6 | | | |
| n | 44 | 50 | 48 |
| Mean (SD) | 3.2 (1.30) | 3.0 (1.18) | 2.6 (1.25) |
| Week 8 | | | |
| n | 45 | 51 | 48 |
| Mean (SD) | 3.0 (1.45) | 3.0 (1.34) | 2.9 (1.50) |
| Week 10 | | | |
| n | 45 | 49 | 47 |
| Mean (SD) | 2.8 (1.40) | 3.2 (1.33) | 3.0 (1.55) |
| Week 12 | | | |
| n | 44 | 50 | 47 |
| Mean (SD) | 2.9 (1.57) | 3.3 (1.47) | 2.9 (1.53) |

### 3.3.4.2. Treatment-Emergent Adverse Events

The overall AE profile was similar among the 3 treatment groups, with the following exceptions: a slightly higher percentage of patients reported TEAEs in the REGN475 0.3 mg/kg group compared with the placebo and REGN475 0.1 mg/kg groups. Serious TEAE's occurred with similar frequency in all treatment groups, and no patients died during the study. One patient (patient 824001) treated with REGN475 0.1 mg/kg withdrew from the study due to a TEAE of moderate Back Pain on study day 66 (Table 19).

**Table 19: Summary of TEAEs (SAF) – R475-PN-0908: Sciatic Pain**

| | Placebo (n = 51) n (%) | REGN475 0.1 mg/kg (n = 53) n (%) | REGN475 0.3 mg/kg (n = 54) n (%) |
|---|---|---|---|
| Number of TEAEs | 45 | 61 | 116 |
| Patients with no TEAEs | 28 (54.9%) | 26 (49.1%) | 19 (35.2%) |
| Patients with at least 1 TEAE | 23 (45.1%) | 27 (50.9%) | 35 (64.8%) |
| Patients with study drug-related TEAEs | 6 (11.8%) | 7 (13.2%) | 13 (24.1%) |
| Patients with serious TEAEs | 1 (2.0%) | 1 (1.9%) | 2 (3.7%) |
| Patients with TEAEs resulting in discontinuation of study drug | | | |
| Patients who discontinued study due to TEAEs | 0 | 1 (1.9%) | 0 |
| Patients who discontinued study due to SAEs | 0 | 0 | 0 |
| Patients who died | 0 | 0 | 0 |

Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

The proportion of patients reporting at least 1 TEAE was similar in the placebo group (45.1%) and the REGN475 0.1 mg/kg (50.9%) group, and was slightly higher (64.8%) in the REGN475 0.3 mg/kg group. The most frequently reported TEAEs were associated with Nervous System Disorders (Paresthesia and Headache) and Musculoskeletal and Connective Tissue Disorders (Arthralgia and Pain in Extremity) and occurred more frequently in the REGN475 0.3 mg/kg treatment group compared with the placebo and REGN475 0.1 mg/kg groups (Table 20).

Among the patients who reported TEAEs, most experienced TEAEs with a maximum severity of mild or moderate. Two patients in the placebo group experienced severe TEAEs of Arthralgia, 1 of whom also experienced a severe TEAE of Paranoia. Four patients in the REGN475 0.3 mg/kg group each experienced 1 severe TEAE: Blood Urea Nitrogen Increased, Chest Discomfort, Major Depression, and Extremity Pain.

**Table 20: Treatment-Emergent Adverse Events Occurring in ≥ 2% of Patients treated with REGN475 by Preferred Term (SAF) – R475-PN-0908: Sciatic Pain**

| MedDRA Preferred Term[a] | Placebo n=51 n (%) | REGN475 0.1 mg/kg (n=53) n (%) | REGN475 0.3mg/kg (n=54) n (%) |
|---|---|---|---|
| Subjects with at least one treatment emergent adverse event | 23(45.1%) | 27(50.9%) | 35(64.8%) |
| Paraesthesia | 0 | 1(1.9%) | 10(18.5%) |
| Arthralgia | 3(5.9%) | 2(3.8%) | 8(14.8%) |
| Pain In Extremity | 1(2.0%) | 0 | 8(14.8%) |
| Headache | 2(3.9%) | 2(3.8%) | 5(9.3%) |
| Anxiety | 0 | 2(3.8%) | 3(5.6%) |
| Nausea | 1(2.0%) | 3(5.7%) | 2(3.7%) |
| Upper Respiratory Tract Infection | 3(5.9%) | 1(1.9%) | 4(7.4%) |
| Nasopharyngitis | 1(2.0%) | 1(1.9%) | 3(5.6%) |
| Decreased Vibratory Sense | 1(2.0%) | 2(3.8%) | 1(1.9%) |
| Dizziness | 1(2.0%) | 2(3.8%) | 1(1.9%) |
| Hypoaesthesia | 0 | 1(1.9%) | 2(3.7%) |
| Muscle Spasms | 0 | 0 | 3(5.6%) |
| Myalgia | 0 | 2(3.8%) | 1(1.9%) |
| Urinary Tract Infection | 1(2.0%) | 2(3.8%) | 1(1.9%) |

[a] In decreasing frequency order based on frequency in REGN475 groups, combined
Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row. MedDRA (Version 13.0) coding dictionary applied

The majority of patients who reported neurosensory or neuromuscular adverse events were in the REGN475 0.3 mg/kg group (Table 20). Paraesthesia and Arthralgia were the most commonly reported events. All events of Paraesthesia were assessed as mild or moderate in severity, and most cases manifested at approximately 2 weeks following treatment and resolved within 1 day to 2 weeks of onset. Arthralgia was reported in a similar proportion of patients in the placebo (5.9%) and REGN475 0.1 mg/kg (3.8%) groups, compared with an incidence of 14.8% in the REGN475 0.3 mg/kg group.

### 3.3.4.3. Serious Adverse Events

Five patients experienced serious TEAEs; 1 patient in the placebo group, and 2 patients each in the REGN475 0.1 mg/kg and 0.3 mg/kg group. Serious TEAEs included Intervertebral Disc Protrusion (2 patients), and Hepatitis B, Major Depression, and Paranoia (1 patient each). None

of the events was considered related to study treatment. A summary of the SAEs reported in this study is presented in Table 21.

**Table 21: Treatment-Emergent Serious Adverse Events (SAF) – R475-PN-0908: Sciatic Pain**

| Patient ID | Event (preferred term) | Onset day | Severity | Causality |
|---|---|---|---|---|
| REGN475 0.1 mg/kg | | | | |
| 818-004 | Hepatitis B | 121 | Severe | Not related |
| 832-016 | Intervertebral disc protrusion | 84 | Moderate | Not related |
| REGN475 0.3 mg/kg | | | | |
| 809-005 | Major depression | 25 | Severe | Not related |
| 832-014 | Intervertebral disc protrusion | 65 | Moderate | Not related |
| Placebo | | | | |
| 809-001 | Paranoia | 68 | Severe | Not related |

Note: Patient 832016 in the REGN475 0.1 mg/kg group had a serious adverse event of herniated nucleus pulposus L4-L5. It occurred 99 days after treatment, and is, therefore, not considered a TEAE.

#### 3.3.4.4. Joint Replacements

One patient treated in this study (placebo) required a knee replacement 15.5 months after dosing. The patient had a history of OA for almost 20 years and had been taking oral prednisone for the prior 2 years for her sciatic pain. After study participation, the patient experienced a slow progression of left knee pain without any specific inciting factors. She underwent left total knee replacement. The post-operative diagnosis was end-stage OA,

## 3.4. Exploratory Study In Vertebral Fracture Pain - ACT11308

**Study Title:** Randomized, Double-Blind, Placebo-Controlled Study of the Effect of a Single Injection of SAR164877 (REGN475) on Reduction of Pain from Vertebral Fracture Associated with Osteoporosis.

### 3.4.1. Study Design Overview

This was a multi-center, randomized, double-blind, prospective, parallel-group study comparing treatment of a single IV injection of REGN475 (0.3 mg/kg) with placebo in patients with pain from vertebral fracture associated with osteoporosis.

### 3.4.2. Study Population

Eligible patients for this study included male and female patients aged ≥ 40 years old and ≤ 80 years old, and with moderate-to-severe pain due to non-traumatic vertebral fracture associated with osteoporosis (diagnosed by radiography as confirmed by the investigator and tenderness on physical palpation over the spinous process of the collapsed vertebra).

### 3.4.3. Study Objectives:

***Primary Objective****:* To demonstrate the activity of the anti-NGF mAb REGN475 on reducing the pain associated with vertebral fracture associated with osteoporosis.

***Secondary Objectives***: To assess the safety, tolerability, PK and immunogenicity profiles of REGN475 in this patient population.

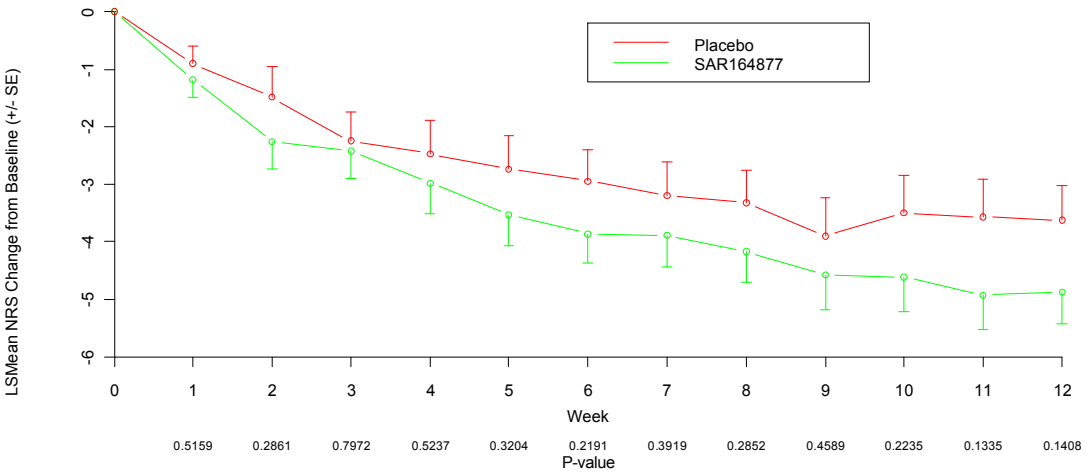
*The ACT11308 study was terminated in November 2010 because of poor enrollment. The LPLV for this study was in January 2011. A total of 41 patients had been randomized and 40 treated at that time (21 active, 19 placebo, 1 withdrew consent before treatment). The target enrollment was 100 patients.*

### 3.4.4. Results: Vertebral Fracture Pain

#### 3.4.4.1. Efficacy

The primary efficacy endpoint was the mean change from baseline to Week 4 in pain intensity-NRS. The baseline value was defined as the average pain intensity-NRS values from Visit 1 and Visit 2. The Week 4 value was defined as the average of daily e-Diary assessments measured during Week 4. Due to the early closeout of the trial, no inferential analyses were performed for the efficacy endpoint. The primary endpoint data are depicted in Figure 11. There were some suggestions of efficacy that warrant further study.

**Figure 11: Change in Weekly Pain Intensity-NRS (LS Mean (by MMRM))**



### 3.4.4.2. Treatment-Emergent Adverse Events

Among patients who received REGN475, 23.8% (5 of 21 patients) experienced at least 1 TEAE compared with 10.5% (2 of 19 patients) who received placebo (Table 22).

Few TEAEs were reported in either treatment group. Among placebo patients, Myalgia and Non-Cardiac Chest Pain were reported in 1 patient each. Among REGN475 patients, Gastroenteritis, Insomnia, Organizing Pneumonia (also reported as a SAE), Nausea, Back Pain, and Influenza-Like Illness were reported by 1 patient each (Table 23).

There were no patients who died during the study. One patient (No. 840/013/006) in the REGN475 group experienced a treatment-emergent SAE, which was reported as Organizing Pneumonia.

There were no patients who experienced TEAEs that led to permanent treatment discontinuation.

**Table 22: Summary of TEAEs (SAF) –ACT11308 (Vertebral Fracture Pain)**

| | **Placebo (n=19) n (%)** | **REGN475 0.3 mg/kg (n=21) n (%)** |
|---|---|---|
| Subjects with no TEAEs | 17 (89.5%) | 16 (76.2%) |
| | | |
| Subjects with at least one TEAE | 2 (10.5%) | 5 (23.8%) |
| | | |
| Subjects with serious TEAEs | 0 | 1 (4.8%) |
| | | |
| Subjects with TEAEs resulting in discontinuation of study drug | 0 | 0 |
| | | |
| Subjects who died | 0 | 0 |

Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

**Table 23: Summary of TEAEs in Patients Treated with REGN475 (SAF) – ACT11308: Vertebral Fracture Pain.**

| MedDRA Preferred Term[a] | Placebo (n=19) n (%) | REGN475 0.3 mg/kg (n=21) n (%) |
|---|---|---|
| Subjects with at least one adverse event | 2 (10.5%) | 5 (23.8%) |
| Back pain | 0 | 1 (4.8%) |
| Gastroenteritis | 0 | 1 (4.8%) |
| Influenza like illness | 0 | 1 (4.8%) |
| Insomnia | 0 | 1 (4.8%) |
| Nausea | 0 | 1 (4.8%) |
| Organizing pneumonia | 0 | 1 (4.8%) |
| Myalgia | 1 (5.3%) | 0 |
| Non-cardiac chest pain | 1 (5.3%) | 0 |

[a] In decreasing frequency order based on frequency in REGN475 groups, combined
Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

#### 3.4.4.3. Serious Adverse Events

Nine days after dosing, patient 840013006 experienced severe Bronchiolitis Obliterans with Organizing Pneumonia. No action was taken in response to the event and the patient recovered 4 days later. The event was considered to be not related to REGN475. The patient completed the study.

#### 3.4.4.4. Joint Replacements

One patient in this study required a hip replacement approximately 10 months after study drug administration (0.3 mg/kg IV). The patient reported developing left hip pain not responsive to conservative treatment. The patient's medical history was remarkable for OA, polymyalgia rheumatica, degenerative disc disease, osteoporosis, vertebral fracture, scoliosis, and acute back pain.

## 3.5. Exploratory Study in Pancreatitis Pain – ACT11286

**Study Title:** Randomized, Double-Blind, Placebo-Controlled Study of the Effect of a Single Injection of SAR164877 (REGN475) on Reduction of Pain from Chronic Pancreatitis.

### 3.5.1. Study Design Overview

This was a multi-center, randomized, double-blind, prospective, parallel-group study comparing treatment with a single IV injection of 0.6 mg/kg of REGN475 with placebo in patients with pain due to chronic pancreatitis. Patients were stratified by alcohol as etiology of chronic pancreatitis.

### 3.5.2. Study Population

Eligible patients for this study included male and female patients aged ≥18 and ≤80 years old. Patients were to have moderate-to-severe abdominal pain due to chronic pancreatitis of at least 6 months duration and at least 2 episodes per month in the preceding 3 months that required analgesia, or at least 1 episode of severe pain that required pain management in an emergency room, a pain specialist, or a hospital setting in the preceding 3 months.

### 3.5.3. Study Objectives:

***Primary Objective:*** To demonstrate the activity of the anti-NGF mAb REGN475 on reducing the pain associated with chronic pancreatitis.

***Secondary Objectives:*** To assess the safety, tolerability, PK and immunogenicity profiles of REGN475 in this patient population.

*The ACT11286 study was terminated in November 2010 because of poor enrollment. The LPLV for this study was January 2011. A total of 15 patients had been randomized at that time (8 active; 7 placebo). The target enrollment was 100 patients.*

### 3.5.4. Results: Safety in Chronic Pancreatitis Pain

#### 3.5.4.1. Treatment-Emergent Adverse Events

The majority of patients in both the placebo (71.4%; 5 of 7 patients) and REGN475 (75.9%; 6 of 8 patients) experienced at least 1 TEAE (Table 24).

Among placebo patients, each TEAE was reported in 1 patient each. Among REGN475 patients, with the exception of Diarrhea, Vomiting, and Arthralgia (reported by 2 patients each), all TEAEs were reported by 1 patient each (Table 25).

There were no patients who died, experienced a treatment-emergent SAE, or experienced TEAEs that led to permanent treatment discontinuation during the study.

**Table 24: Summary of TEAEs (FAS) –ACT11286 (Chronic Pancreatitis Pain)**

| | **Placebo (n=7) n (%)** | **REGN475 0.6mg/kg (n=8) n (%)** |
|---|---|---|
| Subjects with no TEAEs | 2 (28.6%) | 2 (25.0%) |
| | | |
| Subjects with at least one TEAE | 5 (71.4%) | 6 (75.0%) |
| | | |
| Subjects with serious TEAEs | 0 | 0 |
| | | |
| Subjects with TEAEs resulting in discontinuation of study drug | 0 | 0 |
| | | |
| Subjects who died | 0 | 0 |

Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

**Table 25: Summary of TEAEs Reported by Patients Treated with REGN475 (SAF) ACT11286: Chronic Pancreatitis Pain.**

| MedDRA Preferred Term[a] | Placebo (n=7) n (%) | REGN475 0.6mg/kg (n=8) n (%) |
|---|---|---|
| Subjects with at least one adverse event | 5 (71.4%) | 6 (75.0%) |
| Arthralgia | 0 | 2 (25.0%) |
| Diarrhea | 0 | 2 (25.0%) |
| Vomiting | 0 | 2 (25.0%) |
| Abdominal distension | 0 | 1 (12.5%) |
| Abdominal pain upper | 1 (14.3%) | 1 (12.5%) |
| Acne | 0 | 1 (12.5%) |
| Arthritis | 0 | 1 (12.5%) |
| Headache | 1 (14.3%) | 1 (12.5%) |
| Migraine | 0 | 1 (12.5%) |
| Muscle contractions involuntary | 0 | 1 (12.5%) |
| Nausea | 0 | 1 (12.5%) |
| Edema peripheral | 0 | 1 (12.5%) |
| Paraesthesia | 1 (14.3%) | 1 (12.5%) |
| Somnolence | 0 | 1 (12.5%) |
| Abdominal pain | 1 (14.3%) | 0 |
| Coordination abnormal | 1 (14.3%) | 0 |
| Malaise | 1 (14.3%) | 0 |
| Musculoskeletal pain | 1 (14.3%) | 0 |
| Nasopharyngitis | 1 (14.3%) | 0 |
| Pain in extremity | 1 (14.3%) | 0 |
| Panic attack | 1 (14.3%) | 0 |
| Rash | 1 (14.3%) | 0 |
| Thirst decreased | 1 (14.3%) | 0 |
| Tooth abscess | 1 (14.3%) | 0 |
| Upper respiratory tract infection | 1 (14.3%) | 0 |

[a] In decreasing frequency order based on frequency in REGN475 groups, combined
Notes: Treatment Emergent Adverse Events are Adverse Events that occurred between the first dose and end of study. Percentages are based upon the number of patients in each group. A patient can be in more than one row but is represented only once in each row.

### 3.5.4.2. Serious Adverse Events

There were no SAEs reported in this study.

#### 3.5.4.3. Joint Replacements

No patients treated in this study required a joint replacement.

## 3.6. Phase 1 Safety and Pharmacokinetic study – TDU11480

**Study Title:** Randomized, Double-Blind, Placebo-Controlled Study of the Tolerability and Pharmacokinetics of Ascending Single Subcutaneous Doses of SAR164877 (REGN475) in Healthy Male and Female Subjects (TDU11480).

### 3.6.1. Study Population

Eligible subjects for this study were healthy male or female volunteers between 18 and 65 years of age inclusive.

### 3.6.2. Study Objectives:

***Primary Objectives:***

- To assess tolerability following single ascending SC dose administration of REGN475 in healthy male and female subjects
- To assess PK parameters following single ascending SC dose administration of REGN475 in healthy male and female subjects

***Secondary Objective:***

To assess the immunogenicity of REGN475 following single SC dose administration

### 3.6.3. Treatment-Emergent Adverse Events

No subjects discontinued the study due to a TEAE. One subject in the 10 mg dose group reported 1 serious TEAE of severe intensity (Gastroenteritis due to shigella). Two/6 subjects in placebo, 3/6 subjects in the 3 mg dose group, 5/7 subjects in the 10 mg dose group, and 5/6 subjects in the 30 mg dose group reported TEAEs (Table 26). The majority of TEAEs were of mild intensity and all subjects recovered without sequelae. The single severe TEAE was the SAE described in Section 3.6.3.1.

**Table 26: Overview of Adverse Event Profile: Treatment Emergent Adverse Events - Safety Population – TDU11480: Safety and PK Study**

| | | REGN475 | | |
|---|---|---|---|---|
| | **Placebo (N=6) n (%)** | **3 mg (N=6) n (%)** | **10 mg (N=7) n (%)** | **30 mg (N=6) n (%)** |
| Subjects with any TEAE | 2 (33.3%) | 3 (50.0%) | 5 (71.4%) | 5 (83.3%) |
| Subjects with any severe TEAE | 0 | 0 | 1 (14.3%) | 0 |
| Subjects with any treatment emergent SAE | 0 | 0 | 1 (14.3%) | 0 |
| Subjects with any TEAE leading to permanent treatment discontinuation | na | na | na | na |

TEAE: Treatment emergent adverse event, SAE: Serious adverse event , na = not applicable
N = Number of subjects included within each group, n (%) = number and % of subjects with at least one TEAE in each category
Note: An adverse event is considered as treatment emergent if it occurred from the study medication (included) administration until the End of Study visit (included)

The most frequently reported TEAE was Headache (1/6 subject in placebo, and 0/6, 2/7 and 0/6 subjects in 3, 10, and 30 mg groups, respectively).

Three neurosensory events were reported. One patient in each the 10 mg and 30 mg dose groups experienced Decreased Vibratory Sense. One patient in the placebo group experienced Burning Sensation.

All other TEAEs were sporadic among the dose groups. All occurred in a single subject except for Oropharyngeal Pain (one subject in each the 10mg and 30 mg groups), Arthralgia (one subject in each the placebo and 40 mg groups), and Joint Sprain (one subject in each the 3 and 30 mg groups).

### 3.6.3.1. Serious Adverse Events (SAE's)

One female subject (No 840001009) in the 10 mg dose group reported 1 serious TEAE (gastroenteritis due to shigella) of severe intensity on Day 108. The subject recovered on Day 117 without sequelae and completed the study on schedule.

### 3.6.3.2. Joint replacements

No patients treated in this study required a joint replacement.

# 4. REVIEW OF JOINT OR BONE-RELATED CASES

## 4.1. Overview

As of the date of the clinical hold (December 2010), 509 patients had been studied in the REGN475 clinical program. Of these, 357 received active drug and 152 received placebo. In these 509 patients, there have been a total of 14 joint replacement cases identified. Two of the 14 joint replacements were in 2 placebo-treated patients. The other 12 cases occurred in 10 patients treated with REGN475 (Table 27). Ten of the 14 joint replacements occurred 7 or more months after the last dose of study drug. The point estimate for the incidence of patients requiring joint replacement is 1.3% (95% CI: 0.4%, 4.6%) in placebo patients and 2.8% (95% CI: 1.5%, 5.1%) in patients treated with REGN475. Because of uncertainties about the duration of individual patient follow-up and the completeness of post-study information, estimates of the rates of joint replacement per year cannot be calculated.

Prior to the clinical hold being placed on the class of anti-NGF investigational drugs, the REGN475 program was aware of 2 joint replacements in patients in the program. These 2 cases of joint replacement occurred while the R475-0901 study in OA of the knee was still in progress (patients 901-006 and 912-021). Both of these cases were considered by the principal investigators and Regeneron to be consistent with normal progression of disease and not related to study drug. In 1 of these cases (patient 901-006), the joint had been identified for replacement prior to dosing with REGN475.

After the class clinical hold, 12 additional cases of joint replacement were brought to our attention. These cases were identified in response to correspondence that was sent to all patients by their study sites at the time of the anti-NGF class clinical hold. As per FDA request, these letters requested that patients contact their principal investigators if they had experienced any exacerbations in their OA since the study, or if they have had a joint replacement.

The original 2 cases as well as the subsequent 12 cases received by Regeneron are summarized in Table 27, Table 28 and Table 29. Breakdown by study shows that joint replacements were reported in 1 subject in study R475-PN-0817, 9 patients in study R475-PN-0901 (2 patients in this study had both knees replaced), 1 patient in study R475-PN-0908 and one patient in ACT11308 (Table 27). Of the 14 cases, 2 had been treated with placebo and 12 with REGN475. For patients who received REGN475, there was no dose-related pattern to these cases (Table 28). All of the joint replacements were in weight-bearing joints (Table 29).

A listing of joint related events is provided in Table 30.

## 4.2. Summary of Joint-Related Events in the REGN475 Program

**Table 27: Summary of Joint Replacements by Study (SAF)**

| Study | Number of Joint Replacements | | Patients with Joint Replacements n (%) | |
|---|---|---|---|---|
| | Placebo | Active | Placebo N=152 | Active N=357 |
| R475-PN-0817 (FIH) (placebo = 14; active = 42) | 0 | 1 | 0 | 1 (2.4%) |
| R475-PN-0901 (OA Knee) (placebo = 55; active = 160) | 1 | 10 | 1 (1.8%) | 8 (5.0%) |
| R475-PN-0908 (Sciatic pain) (placebo = 51; active = 107) | 1 | 0 | 1 (2.0%) | 0 |
| ACT11286 (Chronic Pancreatitis) (placebo = 7; active = 8) | 0 | 0 | 0 | 0 |
| ACT11308 (Vertebral Fracture) (placebo = 19; active = 21 ) | 0 | 1 | 0 | 1 (4.8%) |
| TDU11480 (PK Study) (placebo = 6; active = 19) | 0 | 0 | 0 | 0 |
| **Total** | **2** | **12** | **2 (1.3%)** | **10 (2.8%)** |

**Table 28: Summary of Joint Replacements by Treatment Group**

| Dose | Number of subjects/patients exposed | Number of Joint Replacements | Patients with Joint Replacements n (%) |
|---|---|---|---|
| Placebo | 152 | 2 | 2 (1.3%) |
| 0.03 mg/kg | 62 | 3 | 2 (3.2%) |
| 0.1 mg/kg | 117 | 2 | 2 (1.7%) |
| 0.3 mg/kg | 139 | 6 | 5 (3.6%) |
| 0.6 mg/kg | 8 | 0 | 0 |
| 1 mg/kg | 12 | 1 | 1 (8.3%) |
| 3 mg | 6 | 0 | 0 |
| 10 mg | 7 | 0 | 0 |
| 30 mg | 6 | 0 | 0 |
| **Total** | **509** | **14** | **12 (2.4%)** |

**Table 29: Joint Replacements Relative to Index Joint**

| | Index Joint | Non-Index Joint | No Index Joint Specified |
|---|---|---|---|
| **Knee** | 7 | 3 | 2[a] |
| **Hip*** | 0 | 1 | 1[b] |
| **Shoulder*** | 0 | 0 | 0 |

[a] One knee replacement in First in Human study in Healthy Volunteers; one knee replacement in Sciatic Pain study.
[b] Hip replacement in the Vertebral Fracture study
[*] Neither hip nor shoulder were index joints in Regeneron or Sanofi studies

**Table 30: Description of Joint-Related Events in the REGN475 Program**

| Patient # Study | Age / Sex | Treatment | Time to Event | Joint Replaced/ Baseline K-L Grade | Relevant History | Severity/ PI Causality | Pathology Report |
|---|---|---|---|---|---|---|---|
| 001-029 (FIH study) | 64/F | 1.0 mg/kg IV (single dose) | Approx. 17 months post-dosing | Knee (L) K-L Grade 3 (NHV – no index) | Obese (body mass index 45); (L) knee OA since 2007. (R) knee OA since 2009 (K-L Grade 2).<br>(L) Knee replacement: 10 November, 2010. | Severe – Not Related | Bone and articular samples (L knee) with changes consistent with DJD and osteopenia |
| 901-006 (OA knee) | 48/M | 0.03 mg/kg IV x 2 (q8 wks) | One month after second dose – during the study. | Knee (R) K-L Grade 3 (Index-R) | Bilateral OA knee x 10 years. TKR (L) in 2004. Multiple arthroscopic surgeries and injections of Cortisone and Synvisc to his right (index) knee over several years.<br>Unknown to the study site, the subject had an MRI performed for a fitted right (index) knee replacement in September 2009 while he was enrolled in the study. The subject had planned to wait until the end of the study to have the procedure done. However, on November 20, 2009, approximately one month after his second dose of study medication, the subject experienced an exacerbation of his right knee pain after twisting his knee during a martial arts class. Following this injury and the subsequent exacerbation of his pain, the subject decided to have the procedure done immediately. | Moderate – Not Related | Pathology not done |

DJD = Degenerative joint disease; K-L = Kellgren-Lawrence; NHV = normal healthy volunteer; PI = Principle investigator

**Table 30: Description of Joint-Related Events in the REGN475 Program (Continued)**

| Patient # Study | Age / Sex | Treatment | Time to Event | Joint Replaced/ Baseline K-L Grade | Relevant History | Severity/ PI Causality | Pathology Report |
|---|---|---|---|---|---|---|---|
| 901-013 (OA study) | 49/F | 0.03 mg/kg IV x 2 (q8 wks) | Knee (L) 7 months post-2nd dose. Knee (R) ~ 12 months post-2nd dose | Knee (L) K-L Grade unknown. Knee (R) K-L Grade 2 (Index-R) | Bilateral knee OA since 2008. Flovent for asthma for 20+ years. At time of study discharge in March of 2010, the patient reported ongoing left knee treatment. X-rays at that time revealed degenerative joint disease (DJD e pain, which was refractory to conservative). TKR (L) was done in June 2010 per patient request. Following (L) TKR, patient reported ongoing (R) knee pain. X-ray showed tri-compartmental degenerative joint disease. TKR in Nov 2010 per patient request. | Moderate – Not Related | TKR (L) pathology: DJD with severe chronic synovitis TKR (R) pathology: DJD with mild, chronic synovitis |
| 902-013 (OA knee) | 58/F | 0.1 mg/kg IV x 2 (q8 wks) | 50 weeks after 2nd dose. | Knee (R) K-L Grade 3 (Index-R) | OA (R) knee since 2006. Cortisone injection (R) knee x 1. Total (R) knee arthroplasty: 07 Dec. 2010. | Severe – Not Related | Pathology not done |
| 907-001 (OA study) | 44/F | 0.3 mg/kg IV (x 1) (Lost to f/u) | Approx. 8.5 months after dose. | Knee (R) K-L Grade 2 (Index-R) | OA of (R) knee since 1982. Total (R) knee replacement : 19 May, 2010. *No radiographs provided for this patient.* | Moderate – Not Related | Pathology (+) for DJD and (–) for osteonecrosis |
| 907-007 (OA study) | 66/F | Placebo (x 1) (Early term) | Approx. 8.5 months after dose. | Knee (R) K-L Grade 3 (Index-R) | Bilateral knee and hip OA since 1995. Reported increase in knee pain post-study Total (R) knee replacement : 13 July, 2010 *No radiographs provided for this patient.* | Moderate – Not Related | Pathology not done |

DJD = Degenerative joint disease; K-L = Kellgren-Lawrence; PI = Principle investigator

**Table 30: Description of Joint-Related Events in the REGN475 Program (Continued)**

| Patient # Study | Age / Sex | Treatment | Time to Event | Joint Replaced/ Baseline K-L Grade | Relevant History | Severity/ PI Causality | Pathology Report |
|---|---|---|---|---|---|---|---|
| 909-004 (OA study) | 72/F | 0.3 mg/kg IV x 2 (q8 wks) | 1 year after 2nd dose. | Knee (R) K-L Grade unknown. Knee (L) K-L Grade 3 (Index-L). | Bilateral OA since 2005. Osteoporosis since 2006. (R) knee was replaced 1 year after second dose (15 Nov. 2010). (L) knee was replaced 6 months later (18 months after drug administration). | Severe – Not Related | Pathology not done |
| 912-021 (OA knee) | 59/F | 0.1 mg/kg IV x 2 (q8 wks) | Seven weeks after 2nd dose - during the study | Hip (R) K-L Grade unknown (non-index joint) | 15-year Hx of bilateral knee OA, 12 year Hx of intermittent (R) hip pain, a 5-year Hx of spinal OA, and a 6-year Hx of osteoporosis. (R) Hip replacement: 8 March, 2010 (7 weeks after second (last) dose). | Severe – Not Related | Pathology not done |
| 929-002 (OA study) | 75/F | 0.3 mg/kg IV x 2 (q8 wks) | Approx. 9 months after 2nd dose. | Knee (R) K-L Grade unknown (Index-L) | Bilateral OA knees since 2003. PI rated TKR as "non-serious" since TKR had been discussed with patient previously. Total (R) knee arthroplasty: 26 July, 2010. | Moderate – Not Related | Pathology not done |
| 917-006 (OA study) | 68/F | 0.3 mg/kg IV x 2 (q8 wks) | 17 months after last dose | Knee (L) K-L Grade 2 (Index-L) | Bilateral OA knees since 2004. In 2010/2011, patient reported increased (L) knee pain. X-ray showed progression of the degenerative changes in the lateral joint compartment. Total (L) knee arthroplasty: 11 May, 2011. Operative findings – DJD. | Severe – Not Related | Pathology not done |

DJD = Degenerative joint disease; K-L = Kellgren-Lawrence; PI = Principle investigator

**Table 30: Description of Joint-Related Events in the REGN475 Program (Continued)**

| Patient # Study | Age / Sex | Treatment | Time to Event | Joint Replaced/ Baseline K-L Grade | Relevant History | Severity/ PI Causality | Pathology Report |
|---|---|---|---|---|---|---|---|
| 818-007 (Sciatica) | 67/F | Placebo (single dose, SC) | Approx. 15.5 months post-dosing | Knee (L) K-L unknown (Sciatic study – no Index) | Sciatica pain (Nov 2009); OA since 1990. (R) knee replaced (Mar 2009), left hip replacement (2008). PO prednisone since 2008 (2mg qD). Acute onset of pain in (L) knee 15 months after study resulting in TKR. (L) Knee replacement: 01 March, 2011. | Severe – Related (Because patient received placebo, Sponsor considered case "not related") | (R) (previous TJR) Mild chronic synovitis and DJD (L) not performed |
| 8400-13006 Vertebral Fracture Study | 77/M | 0.3 mg/kg IV x 1 | 10 months after single dose | Hip (L) K-L unknown (Vertebral Fracture Study – no Index | The patient's medical history was remarkable for osteoarthritis, polymyalgia rheumatica, degenerative disc disease, osteoporosis, hypertension, dyslipidemia, diabetes mellitus type 2, leukocytosis, vertebral fracture, abdominal aortic aneurysm, scoliosis, and acute back pain. Concomitant medications of note included amiodarone, calcium carbonate, vitamin D, vitamin B12, Lovenox, Flonase, glimepiride, insulin, Singulair, Solumedrol, omeprazole, Zofran, torsemide, Coumadin, Taxol, dopamine, oxycodone, and temazepam. (R) hip replacement: 10 May, 2011. | Severe – Related | Left femoral head: overlying degenerated, eroded cartilage tissue with extensive fibrosis, granulation tissue, focal ON, and underlying bone exposure consistent with clinical impression of OA |

DJD = Degenerative joint disease; K-L = Kellgren-Lawrence; ON = osteonecrosis; PI = Principle investigator

## 4.3. Bone Fracture Events in the REGN475 Program

A search of the REGN475 clinical safety database for the preferred terms "fracture", "break", and "broke(n)" yielded no serious cases. Three non-serious cases were identified – two of which had been randomized and one which had not been randomized. A summary of the cases (randomized patients), is provided in Table 31.

Thus, there have been no cases of non-traumatic or atraumatic fracture in the REGN475 clinical program.

**Table 31: Description of Bone Fracture Events**

| Patient | Dose | System Organ Class/High Level Group Term/ Preferred Term/ Verbatim Text | Severity/ PI Causality | Serious | Outcome |
|---|---|---|---|---|---|
| 902-001<br>R475-0901<br>OA Knee | REGN475<br>0.10<br>mg/kg x 2 | Injury, poisoning and procedural complications/Bone and joint injuries/Foot fracture/**acute fracture of lateral sesamoid bone- right foot** | Moderate<br>Not Related<br>*Per chart: Patient tripped over skateboard on the stairs.* | No | Patient left study at Day 109. |
| 922-010<br>R475-0901<br>OA Knee | REGN475<br>0.30<br>mg/kg x 2 | 1. Injury, poisoning and procedural complications/Bone and joint injuries/**Tibia fracture**/fracture of medial tibial plateau- right leg<br><br>2. Injury, poisoning and procedural complications/Bone and joint injuries/Foot fracture/**right foot fracture** | Moderate<br>Not Related<br>*Per chart: Patient missed a step and rolled her foot/ankle. Unable to bear weight.* | No | Patient left study at Day 86. |

## 4.4. Adjudication Review of Joint Replacements in the REGN475 Program

As of August 24th 2011, a total of 14 joint replacements were reported to Regeneron from participants in clinical studies of REGN475. Data from these participants who underwent joint replacement were reviewed in a blinded fashion by an independent adjudication committee. This committee consisted of an Orthopedic Radiologist, a Bone Pathologist and a Rheumatologist:

- Robert Schneider, MD
  Attending Radiologist
  Hospital for Special Surgery
  New York, NY 10021
- Michael J. Klein, MD
  Director of Pathology and Laboratory Medicine
  Hospital for Special Surgery
  New York, NY 10021
- Lee S. Simon, MD
  West Newton, MA 02465

The committee members were provided with clinical narratives, and available radiographic and pathology information for each joint replacement case. Because the majority of these events (12/14) occurred long after the completion of the study, Regeneron was not able to gain access to some patient information (eg, radiographs). In addition, pathology samples were not collected in the majority of cases.

The clinical narratives included medical history; co-morbid conditions; concomitant medications; time frame of participation in the clinical study; information regarding the timing, type of, and reason for joint replacement; and the principal investigator's assessment of relationship to study drug.

Reviewers were asked to evaluate the information for each patient that was relevant to their area of expertise and to complete a questionnaire for each case of joint replacement. The questionnaires asked the reviewers to document whether the evidence provided for each joint replacement was: 1) Normal OA: consistent with the normal progression of OA; 2) Other: *not* consistent with the normal progression of OA; or 3) Insufficient information: the information provided was insufficient to make a determination.

If a reviewer determined that the evidence suggested a diagnosis other than OA, they were then asked to provide the diagnosis that was the most appropriate in their opinion.

Each member first reviewed the data provided to them and came to an independent assessment of each case. After that, a meeting was held with the committee members to review each case and to come to a consensus decision. These decisions were recorded and are summarized in Table 32.

**Table 32: Summary of Adjudication Committee Review – REGN475**

| Patient | Clinical Impression of any/all Adjudicators | Adjudicating Radiologist's Interpretation of Imaging Studies | Adjudicating Pathologist's Interpretation of Slides |
|---|---|---|---|
| **001-029** | Normal OA | Normal OA | Normal OA |
| **901-006** | Normal OA vs. trauma[a] | Normal OA | *No Information* |
| **901-013 (Right)** | Normal OA vs subchondral insufficiency/fracture[a] | Normal OA | Normal progression OA<br>Pathology suggests post-inflammatory OA |
| **901-013 (Left)** | Normal OA vs subchondral insufficiency/fracture[a] | Normal OA | Normal progression OA<br>Pathology suggests post-inflammatory OA |
| **902-013** | Normal OA | Normal OA | *No Information* |
| **907-001** | *Insufficient Information:* Normal OA vs Other[a] | *No Information* | Normal OA |
| **907-007** | Normal OA | *No Information* | *No Information* |
| **909-004 (Left)** | Normal OA | Normal OA | *No Information* |
| **909-004 (Right)** | Normal OA | Normal OA | *No Information* |
| **912-021** | Other: RPOA due to Subchondral fracture | Other: Subchondral fracture / RPOA | *No Information* |
| **917-006** | Normal OA | Normal OA | *No Information* |
| **929-002** | Normal OA | Normal OA | *No Information* |
| **818-007** | Normal OA | Normal OA | Normal OA progression<br>Pathology suggests post-inflammatory OA |
| **840013006** | *Insufficient Information:* Osteoporosis, Osteoarthritis, or Other | *No Information* | *Insufficient Information* |

No information = Either no radiographs or no pathology information could be obtained.
Normal OA = Joint replacement was consistent with the normal progression of OA.
Other = Clinical or radiological course is not consistent with the normal progression of OA.
[a] Different clinical impressions of the clinical and radiologic adjudicators

## 4.5. Summary: Joint- or Bone-Related Cases

The overall incidence of joint replacement in the REGN475 program was 2.8% (14/503). The incidence (3.4%) was nominally higher in those receiving active drug (12/351). The majority of

the joint replacements (83.3%) occurred 7 or more months after the last dose of study drug. Four of the 14 joint replacements occurred in non-index joints – an additional 3 joint replacements occurred in studies where no index joint was specified (FIH, sciatic pain, vertebral fracture pain). Two bone fractures occurred in patients participating in the program, but both were the result of injuries sustained from accidents on stairs and involved bones in the feet. All of the joint replacements were either hip or knee joints. Thus there were no events involving non weight-bearing joints or bones.

Based upon the AE data provided to Regeneron, none of the joint replacement cases were considered to be the result of RPOA or osteonecrosis. However, a review of these cases by the independent adjudication committee did conclude that one of these cases (912-021 – (R) hip) was the result of subchondral fractures that resulted in RPOA. A second case (840013006 – also a hip replacement), was suggested to be the result of severe OA in the setting of osteoporosis/osteopenia. Although a third patient who had bilateral knee replacements was not thought by the clinical review to have normal progression of OA but to have subchondral insufficiency or fracture, the other reviewers concluded that the case was consistent with normal progression of OA and the pathology revealed post-inflammatory OA consistent with seronegative spondyloarthropathy.

Of the 14 events, there were 2 cases deemed by the principal investigators to be causally related to drug treatment. One of these cases was a placebo-treated patient.

In the OA study (R475-PN-0901), baseline screening procedures did not include imaging joints other than the index knee, so the radiographic status of the non-index knee or the hips at the time of the study is not known. In the remaining studies, no joints were imaged as part of the screening process. However, as OA typically involves both knees and hips in affected individuals, it is likely that patients had underlying disease in non-index joints.

Overall, the pattern of notable bone or joint-related AEs either during or within approximately 1 year post-study revealed a single case of RPOA and no cases of osteonecrosis.

# 5. PROPOSED SAFETY AND PHARMACOVIGILANCE PROCEDURES TO ALLOW LIFTING OF CLINICAL HOLD

Data from the tanezumab and fulranumab development programs point to a risk of unanticipated joint deterioration leading to unexpected joint replacements in some patients who have received treatment with an anti-NGF antibody. Moreover, these joints may be associated with pathology that is atypical for OA and there is a question as to whether these occur in patients previously unknown to have OA. In light of these developments, the FDA placed the REGN475 development program on hold along with the tanezumab and fulranumab programs.

A review of the data from the REGN475 program do not suggest that REGN475 use is associated with an increased risk of RPOA, osteonecrosis, joint replacements, or fractures, or with any unique safety concern that would preclude its further study. However, we acknowledge that blinded adjudication committees for the other anti-NGF mAbs have concluded that these molecules are associated with an increased risk of RPOA, and analyses indicate that the risk of RPOA increases with the dose of anti-NGF treatment and is further increased by the concomitant use of chronic NSAIDs. None of the adjudication committees to date have identified a signal for osteonecrosis. The FDA has arranged for the separate review and adjudication of these data and it will be important to know whether FDA-sponsored adjudication yields conclusions similar to the industry-sponsored adjudication.

Clearly the database of patients developed by Regeneron and Sanofi prior to the clinical hold is too small to support or refute the idea that there is a risk of unanticipated joint damage during the use of REGN475. Therefore, although each of these molecules is likely to differ in terms of epitope specificity, affinity for NGF and cross-reactivity for other neurotrophin family members, we believe it prudent to act as if the risks of unanticipated joint deterioration identified with the other anti-NGF mAbs may also be a risk of REGN475. We are interested in learning more about those data at the public advisory committee that the Agency has scheduled.

Our position at Regeneron and Sanofi is that the current data, while providing evidence for the efficacy of anti-NGF therapy, does not support anti-NGF therapy as a general treatment for OA or other pain conditions for which there are adequate treatments; the observed safety signals mentioned above need to be understood to a much greater degree before that could be the case. However, there may be a role for anti-NGF therapy in pain conditions where there is a high unmet need, ie, those for which there are no adequate alternatives. This is predicated on being able to demonstrate a clinically significant benefit over existing options and if there is an acceptable safety profile such that a positive benefit/risk can be established.

For REGN475, we propose a path forward implementing the following strategies:

- **Informed Consent** of patients and appropriate communication of the data and potential risks to investigators, IRBs, and any national health authorities where study is being considered.
- **Risk Minimization** by excluding high risk patients such as those with a history of RPOA, subchondral fractures, or joint dysplasia; minimizing the dose of anti-NGF treatment and excluding concomitant chronic NSAIDs. In non-OA indications, because of the apparent need for higher doses of anti-NGF, we would also exclude patients with evidence of mechanical/structural joint diseases.

- **Restricting Use to High Unmet Need Populations** until such time that the data support the study of additional populations. These include OA and non-OA pain patients (eg, with cancer, neuropathic, thermal injury, or visceral pain conditions) demonstrated to have an insufficient response to standard of care; patients intolerant to or with contraindications (absolute or relative) to standard of care; and patients awaiting TJR surgery (for example, with an anticipated wait of 3 to 9 months).
- **Demonstrating Efficacy in the Selected Populations** that is superior to other options available (eg, in patients with inadequate response to NSAIDs, demonstrating clinically meaningful superiority to NSAIDs).
- **Determining Long-Term General Safety** of the potential long-term consequences of chronic NGF blockade (eg, on peripheral nerves, motor functioning, edema).
- **Defining Joint Safety Risks** that remain after instituting the risk minimization strategies above. This would include ITT follow-up of all patients for the intended duration of the study to 6 months after the last planned dose and assessment of operative complications and outcomes in TJR cases.
- **Additional Risk Factor Characterization** by improving the baseline assessment of joint status and collecting data on potential prognostic indicators such as CTX biomarkers, imaging (eg, ultrasound to determine joint space dimensions), and actimetry to identify factors that might contribute to any residual risks of therapy with REGN475.
- **Risk Management** by discontinuing patients who develop sentinel findings such as subchondral fracture or accelerated joint space narrowing, and having an IDMC assess the emerging data to identify additional risk factors and recommend actions.

These concepts are discussed in greater detail below.

## 5.1. Informed Consent

A primary principal underlying the Declaration of Helsinki is informed consent. Patients, investigators, and IRBs in REGN475 need to be informed of the safety issues that are discussed in this document. We commit to doing so through the written ICF and the Investigator's Brochure.

## 5.2. Risk Minimization

We have been shown compelling analyses of the tanezumab data that suggest the hypothesis that the risk of RPOA with tanezumab was related to tanezumab dose and increased further in patients who were treated with tanezumab in combination with the chronic use of NSAIDs. Thus, one hypothesis is that limiting the dose of anti-NGF treatment and excluding the concomitant use of chronic NSAIDs would result in a risk for RPOA close to that in the general OA population. A second hypothesis is that this RPOA-like joint destruction only occurs in joints that, at baseline, are not normal.

These data and hypotheses provide a basis for a risk minimization strategy to support removal of the clinical hold on REGN475 and a path toward registration that would include testing these hypotheses.

Thus, we propose to limit NSAID use in the REGN475 program. For OA patients, we would assiduously limit the dose of REGN475 as we continue to dose and interval range in Phase 2. For patients with cancer pain or other painful conditions like thermal injury where efficacy may only be seen with higher doses of REGN475, we will exclude patients with evidence of structural diseases of the hips, knees, or shoulders (ie, arthritis or arthroses). Specific recommendations will be proposed after review of data and discussion of these concepts at the Advisory Committee meeting. We would also exclude from all studies patients with joint dysplasia.

We would seek to minimize risk further by excluding patients with previous RPOA or with a history of subchondral fracture as the latter condition may be the initial lesion in many patients who go on to having unanticipated joint deterioration after receiving anti-NGF therapy. At this time, we would not propose to exclude patients with risk factors for osteonecrosis as this does not appear to be the mechanism for unanticipated joint deterioration after treatment with other anti-NGF mAbs.

## 5.3. Restricting Use to High Unmet Need Populations

The current data do not allow us to conclude that the proposed risk minimization steps would eliminate any increase in risk of unanticipated joint deterioration. Therefore, consistent with the other sponsors, we believe it prudent to limit the study of these drugs to those patients who might be expected to derive the greatest benefit.

### 5.3.1. Proposed OA Patient Populations with the Greatest Clinical Need for Anti-NGF Therapy

There are 26 million patients with OA in the United States and more worldwide. At this time, we do not believe that they are all candidates for an anti-NGF agent. We do not, at the current time, envision a general OA pain indication for REGN475. Instead, we are talking about only a subset of patients: patients with pain despite NSAID therapy, patients intolerant to NSAIDs, patients awaiting TJR, and perhaps other subgroups. Our development program will be designed to seek registration in those subsets of OA patients and other unmet medical need pain states by systematically and prospectively studying REGN475 to establish, in those patients, a positive benefit/risk ratio.

#### 5.3.1.1. NSAID Intolerant OA Patients and Patients with OA With Insufficient Response to NSAIDs

Not all patients get sufficient relief from NSAIDs at either the over-the-counter or prescription doses, and many patients are either not good candidates for NSAIDs (e.g., due to difficult to manage hypertension, reduced renal function, history of upper GI ulcers, cardiovascular disease, or a myriad of other conditions) or are not able to tolerate some of the symptomatic side effects of full-dose NSAID therapy. The symptomatic side effects of opioid or tramadol therapy (nausea, constipation, somnolence, dry mouth) are also a common complaint among patients and the primary reason for discontinuing therapy. We believe it would be appropriate to prospectively study the hypothesis that REGN475 provides benefit and has an acceptable safety profile in these patients.

#### 5.3.1.2. Patients Awaiting Joint Replacement Surgery

In the US, delay in joint replacement surgery may be a personal choice or dictated by the health care system. For example, VA and military hospitals have a wait list for elective orthopedic procedures not related to injuries sustained in combat (Department of Veteran Affairs Office of Inspector General 2006). And in some other countries, patients may be on a waiting list for several months. Patients awaiting joint replacement surgery may derive great benefit from anti-NGF analgesia and, since they are already joint replacement candidates, the relative risk of such treatment might be more than acceptable. This is then a second population in which we believe it would be appropriate to prospectively study the hypothesis that REGN475 provides benefit and has an acceptable safety profile.

#### 5.3.1.3. Other OA Subpopulations

There may be other populations of OA patients in whom it might be appropriate to study the efficacy and safety profile of REGN475. One such population is patients whose ambulation is curtailed by OA pain and who would otherwise qualify for joint replacement surgery but who are not medically appropriate for surgery. Although treatment of these patients might initially improve their mobility, it also might lead to additional risk of joint damage and, because these patients are not candidates for joint replacement surgery, they may be worse off in the end. Therefore, we do not currently propose to study REGN475 in these patients and would only seek to do so after additional data have been obtained that support the risk minimization strategies.

### 5.3.2. Proposed Cancer Patient Populations with the Greatest Clinical Need for Anti-NGF Therapy

Patients with primary tumors of breast or prostate carcinoma that have metastasized to bone are frequently confronted with a poor QOL. Skeletal complications as sequelae of metastatic disease manifest themselves in 70% of patients with advanced disease. In addition, skeletal metastases are discovered in >90% of patients who die of breast or prostate carcinoma (Coleman 1997).

Nonsteroidal anti-inflammatory drugs and opioid therapy are the mainstays of treatment for metastatic bone disease. However, as the severity of the pain increases with progression of disease and the frequency of breakthrough pain episodes increases with movement, these therapies become less effective. (Luger 2005)

There are several reports demonstrating that an anti- NGF agent can be effective in reducing bone cancer pain-related behaviors in mice. These reports showed that nearly all nerve fibers that innervate the bone express TrkA and/or p75. These are the receptors through which NGF sensitizes or activates nociceptors (Sevcik 2005; Halvorson 2005). Early administration of anti-NGF can also prevent the pathological reorganization of sensory nerves fibers that has been shown to generate and maintain chronic pain, and therefore, may lead to more effective control of this chronic pain state (Jimenez-Andrade 2011).

Because of the existing unmet medical need for more effective pain management in patients with metastatic bone disease along with the extant evidence demonstrating a role for NGF in the pain associated with these lesions, we propose to test the hypothesis that REGN475 treatment is effective in relieving pain and has an acceptable safety profile in patients with metastatic bone disease. As discussed in Section 5.2, patients with baseline joint findings will be excluded from these studies.

## 5.4. Demonstration of Efficacy Greater Than NSAIDs or Other Standard of Care in Patients with Inadequate Response to Standard of Care

The hypothesis that anti-NGF treatment would provide a clinical benefit to patients who receive inadequate pain relief from NSAIDs requires prospectively demonstrating that, in clinical studies, the clinical efficacy with the anti-NGF agent is meaningfully superior to NSAIDs. To date, no studies have established clinically meaningful superiority of an anti-NGF inhibitor to an NSAID in a prespecified population. We propose for REGN475 to study efficacy in comparison to NSAIDs or other standard of care to test the hypothesis that there is a greater benefit with REGN475 in patients who have an inadequate response to standard of care.

## 5.5. Assessment of the Potential Long-Term Consequences of Chronic NGF Blockade (eg, on Peripheral Nerves, Motor Functioning, Edema)

Safety signals present in the databases of all anti-NGF agents include neurosensory symptoms, myalgia, and arthralgia. These appear early after treatment in susceptible individuals and seem to resolve by the end of the studies. In addition, peripheral edema has been seen with the anti-NGF agents. It is unknown whether there are long-term consequences related to these safety signals. We propose to assess the potential long-term consequences of chronic NGF blockade with REGN475 (eg, on peripheral nerves, motor functioning, edema).

## 5.6. Defining Joint Safety Risks

The previously conducted clinical development programs for all of the anti-NGF mAbs were not designed to capture events that occurred in all patients post-discontinuation from the study. As a result, there is incomplete information on time-to-event and patient-year rates for events of interest. Moreover, because drop-outs did not occur at random but instead because of either lack of efficacy or AEs, there may be missing information that is not balanced between groups and that cannot be imputed accurately. Our future studies will incorporate a number of different assessments and long-term surveillance measures to improve our understanding of the risk of these events and whether the risk is increased with anti-NGF therapies.

The following study design features are proposed to characterize risk for unanticipated joint deterioration with REGN475:

1. Prospective collection of data on events of interest and prespecified blinded adjudication of events

   Joint Safety Evaluation:

   All SAEs of new or worsening joint pain, worsening of arthritis, joint replacement surgery, etc. will be characterized as “unexpected” and “possibly related” unless there is a clear alternative explanation (eg, major trauma). As soon as possible after the event is reported to the investigator, the site should make all reasonable attempts to collect the following information:

   a. An x-ray or other suitable radiographic assessment of the affected joint and submitted to the central reader

b. An x-ray or other suitable radiographic assessment of the contralateral joint and submitted to the central reader
c. Relevant medical history since the prior visit
d. Physical exam including a neurological assessment
e. Samples for laboratory and biomarker evaluation
f. For all joint replacements, request that the affected joint be sent for pathologic examination and provide Regeneron with photomicrographs for adjudication
g. For all joint replacements, provide surgical report and an assessment of the level of difficulty of the procedure
h. For all joint replacements, provide follow-up assessment at 6-months with respect to functional and structural outcome

2. An ITT approach to ascertain and subsequently analyze all events of interest over a specified period from enrollment, including prespecified follow-up of patients who discontinue drug

## 5.7. Additional Risk Factor Characterization

The previously conducted clinical development programs for all of the anti-NGF mAbs were not designed to identify or characterize all the risk factors that could predispose patients to unanticipated joint deterioration (such as RPOA) leading to joint replacement surgery. As a consequence, there is incomplete information about predisposing factors that might increase patients' risk for these events.

The following study design features are proposed to characterize risk factors for unanticipated joint deterioration with REGN475:

1. Baseline phenotyping for all patients, including:
   a. Comprehensive medical history of OA at Screening
   b. Physical exam of all joints at Screening
   c. OA studies: standardized x-rays of both shoulders, hips & knees of all patients, starting at Screening and continuing at specified intervals during and after drug treatment. Patients with radiographic or physical evidence of a disease process other than typical OA would not be allowed to enroll into any study
   d. Non OA studies: standardized x-rays of both shoulders, hips & knees of all patients with history or physical exam suggesting joint disease and exclusion of patients with evidence of structural disease
   e. Central reading and archiving of all x-rays (planned & unplanned)
   f. Biomarker evaluation (eg, vitamin D levels, CTX markers) starting at Baseline and continuing at specified intervals during and after drug treatment
   g. Additional imaging (eg, ultrasonography) starting at Baseline and continuing at specified intervals during and after drug treatment
   h. Document presence of other joint replacement risk factors (eg, steroid use, diabetes, various deformities, etc.)
2. Ongoing biomarker assessment and imaging at fixed intervals and event driven
3. Quantitative data from actimetry and other measures of patients' level of activity

## 5.8. Residual Risk Management

Although one might hope that the risk minimization procedures might eliminate any increased risk of unanticipated joint damage with REGN475, we believe that it is prudent to act as if there may be residual risk that needs to be managed. We propose to institute an IDMC to assess the evolving data from our REGN475 program and help manage any residual risk. Risk minimization steps might include discontinuing patients who exceed a threshold for change in joint space thickness over time or who develop other findings that the ongoing monitoring suggest might provide a sentinel signal for future joint deterioration.

# 6. CONCLUSIONS

Patients with pain have an unmet medical need for new therapeutics. Nerve growth factor is a mechanistically novel target that has shown promise. It has been almost a year since a clinical hold was placed on the class of anti-NGF mAbs because of a concern about osteonecrosis and other joint-replacement events.

Regeneron does not have sufficient information in its database to allay the Agency's concerns about these joint-replacements events. We have been informed that blinded adjudication committees for 2 other anti-NGF mAbs have concluded that these molecules are associated with an increased risk of RPOA. Therefore, based on the limited data available, we believe it prudent to act as if RPOA may be a risk of REGN475. None of the adjudication committees have identified cases of osteonecrosis, and we conclude that osteonecrosis does not represent a risk of REGN475.

Our position at Regeneron and Sanofi is that the current data, while providing evidence for the efficacy of anti-NGF therapy, does not support anti-NGF therapy as a general treatment for OA or other pain conditions for which there are adequate treatments; the observed safety signals mentioned above need to be understood to a much greater degree before that could be the case. However, there may be a role for anti-NGF therapy in pain conditions where there is a high unmet need, ie, those for which there are no adequate alternatives. This is predicated on being able to demonstrate a clinically significant benefit over existing options and an acceptable safety profile such that a positive benefit/risk can be established within this context. Given the unmet need in many pain situations, there should be a path forward for clinical development and ultimate licensing. In that regard, we have seen persuasive information from the other sponsors to support the conclusion that the clinical hold can be lifted. Pfizer and Janssen have proposed populations in which it might be appropriate to renew development and we agree. Specifically, at least with respect to our molecule, we believe that the path forward is to systematically and prospectively test, in the populations that have the greatest unmet clinical need, the risk minimization strategies that have been suggested by the analysis of the tanezumab data. This approach, together with informed consent and the other proposed risk characterization and risk management measures provide a structure in which the clinical hold on REGN475 can be lifted and studies can be resumed to determine if REGN475 provides efficacy and has an acceptable safety profile in patients with high unmet need for analgesia.

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